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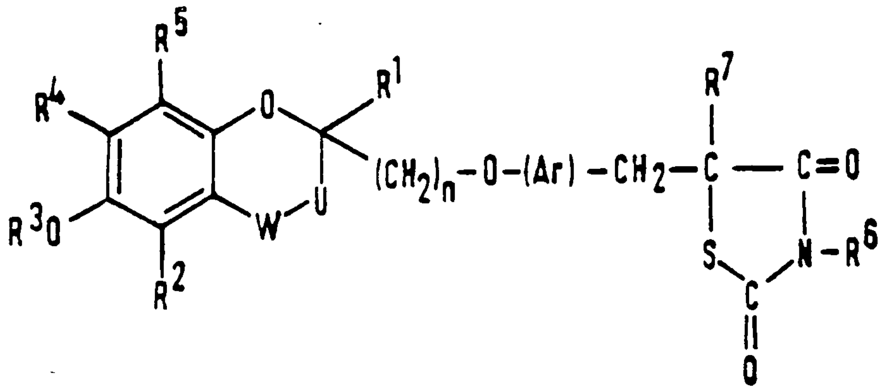
(54) **Thiazolidine derivatives, their preparation and use.**

(57) Compounds of formula (I):

EP 0 207 581 A2



(I)

(in which R^1-R^7 are hydrogen or various organic groups, n is 1-10, Ar is an aromatic group, U is CH_2 or a carbon atom doubly bonded to either one of its adjacent carbons, and W is $>CH_2$, $>C=O$, $>CHOH$, $>C=NOH$ or various derivatives thereof) have the ability to lower the levels of blood lipid peroxides and blood sugars and to inhibit the activity of aldose reductase; they may be used therapeutically for these purposes. They may be prepared by reacting a corresponding compound where the thiazolidine ring is replaced by a group -$C(R^{7a})X$-A (where X is halogen, R^{7a} is similar to R^7 and A is carboxy or similar) with thiourea.

THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND USE

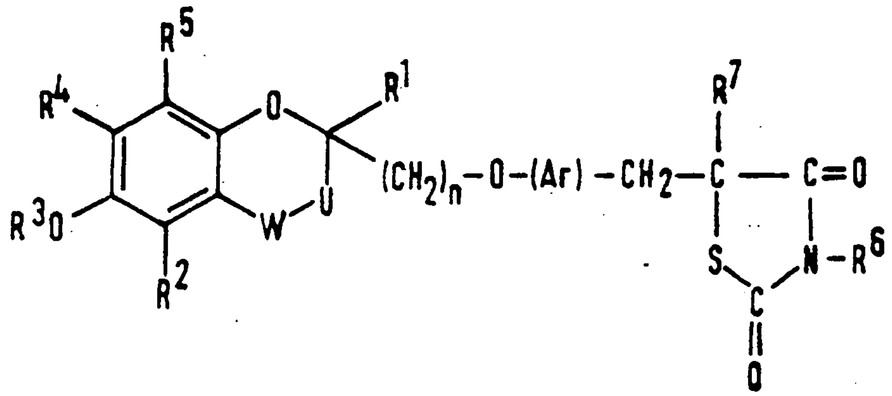
The present invention relates to a series of novel thiazolidine derivatives containing, on a side chain attached to the 5-position, a chroman ring system. The invention also provides processes for preparing these compounds and compositions and methods for using them, especially for reducing blood lipid and blood sugar levels.

Certain thiazolidine derivatives having the ability to lower blood lipid and blood sugar levels are disclosed in European Patent Publication No. 8203 and in Chem. Pharm. Bull., 30, 3580 (1982). Certain of the thiazolidine derivatives disclosed in these documents have the ability to lower blood lipid and blood sugar levels, although these compounds are rather toxic.

In copending European Patent Publication No. 0139421 there are also disclosed some related thiazolidine derivatives having a similar class of activities; some of these prior compounds may also be used as starting materials to prepare the compounds of the invention.

We have now discovered a series of thiazolidine derivatives which have the ability to improve the metabolism of blood lipids, that is to say they reduce the level of blood lipid peroxides, blood triglycerides, blood cholesterol and blood sugar, whilst having a very low toxicity. The compounds of the invention also have the ability to inhibit the activity of aldose reductase.

The compounds of the present invention may be represented by the formula (I):



(I)

in which:

R^1 represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_7-C_{13} aralkyl group;

R^2 represents a hydrogen atom or a C_1-C_8 alkyl group;

R^3 represents a hydrogen atom, a C_1-C_{25} alkanoyl group, a C_3-C_{25} alkenoyl group, a C_3-C_{25} alkynoyl group, a substituted C_1-C_{25} alkanoyl, C_3-C_{25} alkenoyl or C_3-C_{25} alkynoyl group having at least one substituent selected from the group consisting of substituents (a), an aromatic acyl group, a heterocyclic acyl group, a group of formula $-SO_2R^8$ where

R^8 represents a hydrogen atom, an aralkyl group where the alkyl part is C_1-C_3 alkyl, a C_1-C_6 alkyl group or a C_1-C_6 alkyl group having at least one substituent selected from th group consisting of hydroxy groups and C_1-C_6 alkoxy groups,

a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one substituent selected from the group consisting of substituents (b);

R^4 represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_1-C_8 alkoxy group;

R^5 represents a hydrogen atom, a C_1-C_8 alkyl group or a C_1-C_8 alkoxy group;

R^6 and R^7 are independently selected from the group consisting of hydrogen atoms, C_1-C_{10} alkyl groups and substituted C_1-C_{10} alkyl groups having at least one substituent selected from the group consisting of substituents (b);

Ar is a divalent group selected from the group consisting of divalent carbocyclic aromatic groups and divalent heterocyclic aromatic groups;

W represents a $-CH_2$-group, a $>C=O$ group, a

group of formula >CH-OR^{11}

wherein R^{11} represents a hydrogen atom, a C_1-C_{23} alkanoyl group, a C_3-C_{23} alkenoyl group, a C_3-C_{23} alkynoyl group, a substituted C_1-C_{23} alkanoyl, C_3-C_{23} alkenoyl or C_3-C_{23} alkynoyl group having at least one substituent selected from the group consisting of substituents (a), an aromatic acyl group, a heterocyclic acyl group, a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one substituent selected from the group consisting of substituents (b),

or a group of formula >C=N-O-R^{12}

in which R^{12} represents a hydrogen atom, a C_1-C_{10} alkyl group, a C_1-C_{10} alkyl group, having at least one substituent selected from the group consisting of substituents (b), a C_1-C_{23} alkanoyl group, a C_3-C_{23} alkenoyl group, a C_3-C_{23} alkynoyl group, a substituted C_1-C_{23} alkanoyl, C_3-C_{23} alkenoyl or C_3-C_{23} alkynoyl group having at least one substituent selected from the group consisting of substituents (a), an aromatic acyl group, a heterocyclic acyl group or a group of formula -CONR^{9}R^{10} where

R^9 and R^{10} are independently selected from the group consisting of hydrogen atoms and C_1-C_6 alkyl groups or R^9 and R^{10}, together with the nitrogen atom to which they are attached, represent a heterocyclic group having from 5 to 7 ring atoms of which from 1 to 3 atoms, including said nitrogen atom, are hetero-atoms selected from the group consisting of nitrogen, oxygen and sulphur hetero-atoms, said heterocyclic group being unsubstituted, or, where said ring atoms include an additional nitrogen hetero-atom, said additional nitrogen atom being unsubstituted or having a single substituent selected from the group consisting of substituents (e);

U represents a -CH_2-group;

or

W and U together represent a group of formula -CH=CH-;

or

when W represents a carbonyl group or said group of formula >C=N-OR^{12}, U, R^1 and the carbon atom to which R^1 is attached together represent a group of formula -CH=C<;

<u>n</u> is an integer of from 1 to 3;

said aryl groups and the aryl parts of said aralkyl, aralkyl xycarbonyl, aromatic acyl, aromatic acyloxy and divalent aromatic groups being C_6-C_{10} carbocyclic aryl groups which are unsubstituted or have at least one substituent selected from the group consisting of substituents (c);

said heterocyclic groups, heterocyclic parts of said heterocyclic acyl and acyloxy groups and said divalent heterocyclic aromatic groups have from 5 to 10 ring atoms, of which from 1 to 5 are hetero-atoms selected from the group consisting of nitrogen, oxygen and sulphur hetero-atoms, said heterocyclic groups being unsubstituted or having at least one substituent selected from the group consisting of substituents (d);

said substituents (a) being selected from the group consisting of aryl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups and aralkyloxycarbonyl groups;

said substituents (b) being selected from the group consisting of hydroxy groups, C_1-C_6 alkoxy groups, aryl groups, C_1-C_{23} alkanoyloxy groups, C_3-C_{23} alkenoyloxy groups, C_3-C_{23} alkynoyloxy groups, substituted C_1-C_{23} alkanoyloxy, C_3-C_{23} alkenoyloxy or C_3-C_{23} alkynoyloxy groups having at least one substitutent selected from the group consisting of substituents (a), aromatic acyloxy groups, heterocyclic acyloxy groups, groups of formula -COOR^8 where R^8 is as defined above and groups of formula -CONR^{9}R^{10} where R^9 and R^{10} are as defined above;

said substituents (c) being selected from the group consisting of C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups, C_1-C_6 alkyl groups having at least one halogen substituent, halogen atoms, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups in which each alkyl part is C_1-C_6, nitro groups, cyano groups, groups of formula -CONR$_2$ where R represents a C_1-C_6 alkyl group or an aryl group and hydroxy groups;

said substituents (d) being selected from the group consisting of C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups and doubly bonded oxygen atoms; and

said substituents (e) being selected from the group consisting of C_1-C_6 alkyl groups, C_1-C_6 alkanoyl groups, C_3-C_6 alkenoyl groups and C_3-C_6 alkynoyl groups;

and pharmaceutically acceptable salts thereof.

Certain of the compounds defined above are covered by our prior EP-A 0139421. The present invention only claims as new compounds those compounds defined above in which:

(α) where: R^3 represents said hydrogen atom, an unsubstituted C_1-C_6 alkanoyl group, an unsubstituted C_3-C_6 alkenoyl group, an unsubstituted C_3-C_6 alkynoyl group, said aromatic acyl group, said heterocyclic acyl group, an aralkanoyl group or an aralkenoyl group; and R^6 and R^7 both represent hydrogen atoms; and Ar represents a p-phenylene group; and W represents a group of formula $>CH_2$, $>C=O$ or $>CH$-OR^{11x} (wherein R^{11x} represents a hydrogen atom, an unsubstituted C_1-C_6 alkanoyl group, an unsubstituted C_3-C_6 alkenoyl group, an unsubstituted C_3-C_6 alkynoyl group, said aromatic acyl group, said heterocyclic acyl group, an aralkanoyl group or an aralkenoyl group); and U represents said group of formula $> CH_2$,

then

(i) when R^1 represents a hydrogen atom or a C_1-C_5 alkyl group, R^4 represents a C_6-C_{10} alkyl group, and

(ii) when R^4 represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, R^1 represents a C_6-C_{10} alkyl group or said C_7-C_{13} aralkyl group; or

(β) where: R^1 and R^2 are independently selected from the group consisting of hydrogen atoms and C_1-C_5 alkyl groups; and R^4 and R^5 are independently selected from the group consisting of hydrogen atoms, C_1-C_5 alkyl groups and C_1-C_5 alkoxy groups; and Ar represents a p-phenylene group; and W is a group of formula $>CH_2$, $>C=O$ or $>CH$-OR^{11x} (where R^{11x} is as defined above); and U represents said group of formula $>CH_2$; and n is an integer from 1 to 3.

then

at least one of R^3, R^6 and R^7 represents said alkyl or substituted alkyl group.

The invention also provides processes for preparing the compounds of the invention, as described in more detail hereafter.

The invention still further provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

The compounds of the invention can be used for reducing blood lipid and blood sugar levels in an animal, especially a mammal, e.g. a human being, by administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In the compounds of the invention, where R^1, R^2, R^6, R^7, R^{11} or R^{12} represents a C_1-C_{10} alkyl group, this may be a straight or branched chain group and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, hexyl, isohexyl, neohexyl, 1-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 1-methyl-1-ethylpropyl, heptyl, 1-methylhexyl, 1-propylbutyl, 4,4-dimethylpentyl, octyl, 1-methylheptyl, 2-ethylhexyl, 5,5-dimethylhexyl, nonyl, decyl, 1-methylnonyl, 3,7-dimethyloctyl and 7,7-dimethyloctyl groups.

Where R^1 or R^5 represents an aralkyl group, this may be substituted or unsubstituted and is a C_7-C_{13} aralkyl group, for example a substituted or unsubstituted benzyl, phenethyl, 3-phenylpropyl or 4-phenylbutyl group. Examples of suitable substituents include: C_1-C_4 alkyl groups, particularly the methyl, ethyl and propyl groups; C_1-C_4 alkoxy groups, particularly the methoxy, ethoxy and propoxy groups; and halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms.

Where R^2 represents an alkyl group, this may be a C_1-C_5 alkyl group, for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl group.

Where the acyl group represented by R^3, R^{11} or R^{12} is an aliphatic acyl group, this may be a saturated or unsaturated group (the terms "saturated" and "unsaturated" referring to the carbon-carbon bonds) having up to 23 carbon atoms and is thus a C_1-C_{23} alkanoyl, C_3-C_{23} alkenoyl or C_3-C_{23} alkynoyl group, which may be unsubstituted or may have one or more substituents selected from substituents (a), for example selected from the group consisting of aryl groups, carboxy groups, C_2-C_6 alkoxycarbonyl groups or aralkyloxycarbonyl groups. Examples of such aliphatic acyl groups include the formyl, acetyl, propionyl, propioloyl, butyryl, isobutyryl, pivaloyl, hexanoyl, acryloyl, methacryloyl, crotonoyl, octanoyl, decanoyl, tridecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, 2,6,10,14-tetramethylnonadecanoyl and icosanoyl groups. Such groups may be unsubstituted or have one or more (preferably one) substituents as defined above. Suitable aryl substituents include the phenyl and 1-or 2-naphthyl groups, especially the phenyl group, which may themselves be unsubstituted or have one or more substituents selected from substituents (c), especially C_1-C_5 alkyl groups, C_1-C_5 alkoxy groups, halogen atoms, hydroxy groups, nitro groups, amino groups and dialkylamino groups where each alkyl part is C_1-C_4; specific xamples of the resulting araliphatic acyl groups are given hereafter. Suitable alkoxycarbonyl groups (as substituents on these acyl groups) include straight or branched chain C_2-C_6 groups (i. . the

alkoxy part is C_1-C_5), such as th methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl,. pentyloxycarbonyl and isopentyloxycarbonyl groups. Suitable aralkyloxycarbonyl groups include those where the aralkyl part is as exemplified above in relation to R^1.

Examples of the alkanoyl, alkenoyl and alkynoyl groups which may be included in substituents (e) are those unsubstituted acyl groups exemplified above and having up to 5 carbon atoms.

Where R^3, R^{11} or R^{12} represents an aromatic acyl group, this is preferably an arylcarbonyl group in which the aryl part is as defined above, but is preferably a phenyl or naphthyl (1-or 2-naphthyl) group, which may be unsubstituted or may have one or more of the substituents (c) defined above. Examples of such aromatic acyl groups include the benzoyl, 4-nitrobenzoyl, 3-fluorobenzoyl, 2-chlorobenzoyl, 4-aminobenzoyl, 3-dimethylaminobenzoyl, 2-methoxybenzoyl, 3,4-dichlorobenzoyl, . 3,5-di-t-butyl-4-hydroxybenzoyl and 1-naphthoyl groups.

Where R^3, R^{11} or R^{12} represents a heterocyclic acyl group, this is preferably a heterocyclic-carbonyl group, in which the heterocyclic part is as defined above, but is preferably a heterocyclic group having from 5 to 8, and more preferably 5 or 6, ring atoms, of which from 1 to 3, and preferably 1, are hetero-atoms selected from the group consisting of nitrogen, oxygen and sulphur hetero-atoms. Such heterocyclic groups may be unsubstituted or may have at least one substituent (d), as defined above. Examples of such heterocyclic acyl groups include the 2-furoyl, 3-thenoyl, 3-pyridinecarbonyl and 4-pyridinecarbonyl groups.

Where R^3, R^{11} or R^{12} represents an araliphatic acyl group, this is preferably an aralkanoyl or aralkenoyl group, in which the aryl part is as defined above, but is preferably a phenyl or naphthyl group, more preferably a phenyl group, which may be unsubstituted or may have one or more of the substituents (c) defined above. The alkanoyl or alkenoyl part is preferably a C_2-C_6 alkanoyl or C_3-C_6 alkenoyl group, more preferably an acetyl, propionyl or acryloyl group. Examples of such araliphatic acyl groups include the phenylacetyl, α-(4-chlorophenyl)acetyl, 3-phenylpropionyl and cinnamoyl groups.

Where R^3, R^6, R^7, R^{11} or R^{12} represents a substituted alkyl group, this is a C_1-C_{10} alkyl group having at least one of the substituents defined above as substituents (b). The parent alkyl group may be any one of those exemplified abov . Examples of the substituents include:

hydroxy groups;

alkanoyloxy, alkenoyloxy and alkynoyloxy groups - (which may be substituted or unsubstituted), aromatic acyloxy groups and heterocyclic acyloxy groups, examples of which are the acyloxy groups corresponding to the acyl groups exemplified above in relation to R^3, R^{11} and R^{12};

carboxy groups (i.e. -COOR^8 where R^8 is hydrogen);

aralkyloxycarbonyl groups (i.e. -COOR^8 where R^8 is aralkyl), e.g. where the aralkyl part is as exemplified above in relation to R^1;

C_2-C_6 alkoxycarbonyl groups (i.e. -COOR^8 where R^8 is C_1-C_5 alkyl) e.g. as exemplified above in relation to substituents on aliphatic acyl groups represented by R^3, R^{11} and R^{12};

C_2-C_6 hydroxyalkoxycarbonyl groups (i.e. -COOR^8 where R^8 is C_1-C_5 hydroxyalkyl), e.g. hydroxy-substituted analogues of the alkoxycarbonyl groups mentioned above, especially 2-hydroxyethoxycarbonyl, 3-hydroxypropoxycarbonyl and 2-hydroxypropoxycarbonyl groups;

alkoxyalkoxycarbonyl groups (i.e. -COOR^8 where R^8 is C_1-C_5 alkyl having a C_1-C_5 alkoxy substituent), e.g. alkoxy-substituted analogues of the alkoxycarbonyl groups mentioned above, especially methoxymethoxycarbonyl, ethoxymethoxycarbonyl, 2-methoxyethoxycarbonyl, 2-ethoxyethoxycarbonyl, 2-propoxyethoxycarbonyl, 1-methoxyethoxycarbonyl, 3-methoxypropoxycarbonyl, 3-ethoxypropoxycarbonyl, 3-propoxypropoxycarbonyl, 3-t-butoxypropoxycarbonyl, 2-methoxy-1-methylethoxycarbonyl, 2-ethoxy-1-methylethoxycarbonyl, 3-isopropoxypropoxycarbonyl, 4-methoxybutoxycarbonyl, 4-ethoxybutoxycarbonyl, 4-propoxybutoxycarbonyl, 4-butoxybutoxycarbonyl, 4-t-butoxybutoxycarbonyl, 5-methoxypentyloxycarbonyl and 5-ethoxypentyloxycarbonyl groups;

carbamoyl groups (i.e. -CONR^{9}R^{10} where $R^9 = R^{10} = H$);

mono-and di-alkylcarbamoyl groups (i.e. the groups -CONR^{9}R^{10} where one or both of R^9 and R^{10} represents a C_1-C_5 alkyl group), e.g. the methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, sec-butylcarbamoyl, pentylcarbamoyl, isopentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl, dipentylcarbamoyl, N-methyl-N-ethylcarbamoyl, N-methyl-N-propylcarbamoyl and N-ethyl-N-propylcarbamoyl groups;

and

nitrogen-containing heterocyclic acyl groups (i.e. -$CONR^9R^{10}$ where R^9, R^{10} and the nitrogen atom together form an optionally substituted heterocyclic group), for example the 1-pyrrolylcarbonyl, 1-imidazolylcarbonyl, 3-thiazolidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-pyrrolinylcarbonyl, 1-imidazolinylcarbonyl, 1-imidazolidinylcarbonyl, 3-methyl-1-imidazolidinylcarbonyl, 3-ethyl-1-imidazolidinylcarbonyl, 3-t-butyl-1-imidazolidinylcarbonyl, 3-acetyl-1-imidazolidinylcarbonyl, 3-butyryl-1-imidazolidinylcarbonyl, 3-valeryl-1-imidazolidinylcarbonyl, 3-pivaloyl-1-imidazolidinylcarbonyl, piperidinocarbonyl, 1-piperazinylcarbonyl, 4-methyl-1-piperazinylcarbonyl, 4-ethyl-1-piperazinylcarbonyl, 4-propyl-1-piperazinylcarbonyl, 4-butyl-1-piperazinylcarbonyl, 4-pentyl-1-piperazinylcarbonyl, 4-t-butyl-1-piperazinylcarbonyl, 4-acetyl-1-piperazinylcarbonyl, 4-formyl-1-piperazinylcarbonyl, 4-propionyl-1-piperazinylcarbonyl, 4-acryloyl-1-piperazinylcarbonyl, 4-methacryloyl-1-piperazinylcarbonyl, 4-propioloyl-1-piperazinylcarbonyl, 4-butyryl-1-piperazinylcarbonyl, 4-isovaleryl-1-piperazinylcarbonyl and morpholinocarbonyl groups.

Where R^4 represents an alkyl group, this has from 1 to 10 carbon atoms and is a straight or branched chain group. Certain examples of such alkyl groups have been given above in relation to such groups which may be represented by R^1. However, preferred examples of alkyl groups which may be represented by R^4 include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, hexyl, 1,1-dimethylbutyl, 1,3-dimethylbutyl, heptyl, 1,1-diethylpropyl, octyl, 1-methylheptyl, 2-ethylhexyl, 1,1,3,3-tetramethylbutyl, nonyl, decyl and 3,7-dimethyloctyl groups.

Where R^4, R^5 or substituent (b) represents an alkoxy group, this may have from 1 to 5 carbon atoms and may be a straight or branched chain group. Examples of such alkoxy groups include the methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy and pentyloxy groups.

Where R^5 or substituent (e) represents an alkyl group, this may have from 1 to 5 carbon atoms and may be a straight or branched chain group. Examples of such alkyl groups which may be represented by R^5 are included amongst the alkyl groups which may be represented by R^1 or by R^4. However, preferred alkyl groups which may be represented by R^5 include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and isopentyl groups.

Where Ar represents a divalent carbocyclic aromatic group, this may be substituted or unsubstituted and has from 6 to 10 ring carbon atoms. Examples of such divalent aromatic groups include the p-phenylene, o-phenylene and m-phenylene groups. Where such a group is substituted, it may have at least one of the substituents (c) defined above, but preferably C_1-C_5 alkyl groups (e.g. the methyl, ethyl, propyl, isopropyl, butyl or pentyl groups) or C_1-C_5 alkoxy groups (e.g. the methoxy, ethoxy, isopropoxy, t-butoxy or pentyloxy groups).

Where Ar represents a divalent aromatic heterocyclic group, the heterocyclic group is preferably a pyridine, furan, thiophene or pyrrole ring, which may be unsubstituted or have at least one of the substituents (d) defined above, and the two free valences may be in a variety of positions. Specific examples of such groups are as follows, in which the first number given denotes the position of attachment of the heterocyclic group to the group of formula $-(CH_2)_n-O-$, whilst the second number given denotes the position of attachment of the heterocyclic group to the $-CH_2-$thiazolidine group: the pyrid-2,3-diyl, pyrid-2,4-diyl, pyrid-2,5-diyl, pyrid-2,6-diyl, pyrid-3,4-diyl, pyrid-3,5-diyl, pyrid-3,6-diyl, pyrid-3,2-diyl, pyrid-4,3-diyl, pyrid-4,2-diyl, furan-2,3-diyl, furan-2,4-diyl, furan-2,5-diyl, furan-3,2-diyl, furan-4,2-diyl, thien-2,3-diyl, thien-2,4-diyl, thien-2,5-diyl, thien-3,2-diyl, thien-4,2-diyl, pyrrol-2,3-diyl, pyrrol-2,4-diyl, pyrrol-2,5-diyl, pyrrol-3,2-diyl or pyrrol-4,2-diyl groups. Such groups may be unsubstituted or, if desired, may have at least one, and preferably only one, substituent selected from those substituents (d) defined above, but preferably C_1-C_5 alkyl groups (e.g. the methyl,ethyl, isopropyl, t-butyl or pentyl groups) or C_1-C_5 alkoxy groups (e.g. the methoxy, ethoxy, isopropoxy, t-butoxy or pentyloxy groups).

W may represent a methylene ($-CH_2-$) group, a carbonyl ($>C=O$) group, a group of formula $>CH-OR^{11}$ (in which R^{11} is as defined above) or a group of formula $>C=NOR^{12}$ (where R^{12} is as defined above and may be the same as or different from the atom or group represented by R^3). Examples of the acyl and alkyl groups which may be represented by R^{11} and R^{12} are as given above. Where R^{12} represents a group of formula $-CONR^9R^{10}$, i.e. a carbamoyl or mono-or di-alkylcarbamoyl group, examples of such groups are as given in relation to the similar groups which may be represented by substituents (b).

Alternatively, W and U may together form a double bond, e.g. as illustrated by the compounds of formula (I-12) described hereafter.

U preferably represents a methylene group. However, as mentioned above, it may form a double bond with W, or, when W represents a carbonyl group or a group of formula $>C=N-OR^{12}$, U may,

together with R^1 and the carbon atom to which the group represented by R^1 is attached, form a group of formula -CH=C<, .g. as illustrated in the compounds of formulae (I-8) to (I-11), defined hereafter.

Where substituent (c) is a C_1-C_6 alkyl group having at least one halogen substituent, the alkyl part may be any one of those C_1-C_6 alkyl groups defined above in relation to R^5, both straight and branched chain groups. The resulting haloalkyl group may have one or more halogen atoms (e.g. fluorine, chlorine, bromine or iodine atoms) up to complete perhalogenation. Examples of such groups include the chloromethyl, dichloromethyl, iodomethyl, bromomethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2-fluoroethyl, 1,2-dibromoethyl, 1,2-dichloroethyl, 2,2-dichloroethyl, 2,2-difluoroethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2,2,2-tribromoethyl, 1,2,2-trichloroethyl, 1,2,3-trichloropropyl, 4-chlorobutyl and 5-fluoropentyl groups, of which the trifluoromethyl group is preferred.

Where the compounds of the present invention contain an acidic group in their molecule, for example where they contain a carboxy group or where R^3 represents a hydrogen atom and the resulting hydroxy group is of an acidic character or where R^3 represents a sulpho ($-SO_3H$) group, then the compounds of the invention may form salts with cations. There is no limitation upon the nature of such salts, provided that, where they are to be used for therapeutic purposes, they are pharmaceutically acceptable, which, as is well-known in the art, means that they do not have reduced activity (or unacceptably reduced activity) or increased toxicity (or unacceptably increased toxicity) compared with the free compound of formula (I). Where, however, they are to be used for non-therapeutic purposes, e.g. as intermediates in the preparation of other compounds, even this limitation does not apply. Suitable salts include, for example: alkali metal salts, such as the sodium or potassium salts; alkaline earth metal salts, such as the calcium or magnesium salts; other metal salts, such as the aluminium or iron salts; salts with basic amino acids, such as the lysine or arginine salts; ammonium salts; and salts with organic amines, such as the cyclohexylammonium, diisopropylammonium and triethylammonium salts.

The compounds of the invention may also, depending upon the particular substituents, contain basic groups in their molecules and, in such a case, they can also form acid addition salts. As with the salts mentioned above, there is no particular limitation on the nature of the acid forming such a salt, provided that, where the compound is to be used for therapeutic purposes, the resulting salt is pharmaceutically acceptable. Examples of suitable acids include: inorganic acids, such as hydrochloric acid, sulphuric acid, nitric acid or phosphoric acid; organic carboxylic acids, such as acetic acid, tartaric acid, maleic acid, fumaric acid, malic acid, succinic acid, glutamic acid or aspartic acid; and organic sulphonic acids, such as p -toluenesulphonic acid or methanesulphonic acid.

Preferred classes of compound of the present invention are as follows:

(1) Compounds of formula (I) in which:

R^1 represents a hydrogen atom or a C_1-C_{10} alkyl group;

R^2 represents a hydrogen atom or a C_1-C_3 alkyl group;

R^3 represents a hydrogen atom, a sulpho group, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one substituent selected from the group consisting of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one substituent selected from the group consisting of substituents (g), a group of formula R^{13}-$(CH_2)_m$-CO-, where

R^{13} represents a phenyl group or a phenyl group having at least one substituent selected from the group consisting of substituents (g), and m is an integer from 1 to 5,

a group of formula Het-CO-, where

Het represents a heterocyclic group having 5 or 6 ring atoms, of which from 1 to 3, and preferably 1, are hetero-atoms selected from the group consisting of nitrogen, oxygen and sulphur hetero-atoms, said heterocyclic group being unsubstituted or having at least one substituent selected from the group consisting of C_1-C_6 alkyl groups,

a C_1-C_6 alkyl group, a C_1-C_6 alkyl group substituted by a group of formula $-COOR^{6a}$, where

R^{6a} represents a hydrogen atom, a C_1-C_6 alkyl group or an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_6,

a C_2-C_6 hydroxyalkyl group, an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_6, a C_2-C_6 alkyl group substituted by a group of formula $-O-CO-R^{53}$, wher

R^{53} represents a C_1-C_{10} alkyl group, a phenyl group, a phenyl group having at least one substituent s lected from the group consisting of substituents -

(g) or a heterocyclic group Het, as defined above,

or a C_1-C_3 alkyl group substituted by a single substituent selected from the group consisting of substituents (h);

said substituents (f) are selected from the group consisting of phenyl groups, carboxy groups, C_2-C_6 alkoxycarbonyl groups and benzyloxycarbonyl groups;

said substituents (g) are selected from the group consisting of C_1-C_5 alkyl groups, trifluoromethyl groups, C_1-C_5 alkoxy groups, halogen atoms, nitro groups, amino groups, hydroxy groups and dialkylamino groups where each alkyl part is C_1-C_4;

said substituents (h) are selected from the group consisting of alkylcarbamoyl groups where the alkyl part is C_1-C_4, dialkylcarbamoyl groups where each alkyl part is C_1-C_4, 1-pyrrolidinylcarbonyl groups, piperidinocarbonyl groups and morpholinocarbonyl groups;

R^4 represents a C_1-C_{10} alkyl group or a methoxy group;

R^5 represents a hydrogen atom, a C_1-C_5 alkyl group or a methoxy group;

R^6 and R^7 are independently selected from the group consisting of hydrogen atoms, C_1-C_5 alkyl groups, C_1-C_5 alkyl groups substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined above, C_2-C_5 hydroxyalkyl groups, C_1-C_5 alkyl groups substituted by a C_1-C_5 alkoxy group, C_2-C_5 alkyl groups substituted by a group of formula $-O-CO-R^{8b}$ where R^{8b} is as defined above, and C_1-C_3 alkyl groups having a single substituent selected from the group consisting of substituents (h);

Ar represents a <u>o</u>-phenylene, <u>m</u>-phenylene or <u>p</u>-phenylene group or a pyridine-diyl group which is attached to the part of said compound of formula (I) of formula $-(CH_2)_n-O-$ at its 2-position and is attached to the $-CH_2$-thiazolidine group at its 5-or 6-position, said phenylene and pyridine-diyl groups being unsubstituted or having a C_1-C_3 alkyl substituent;

W represents a group of formula $-CH_2-$, $>C=O$, $>CH-OR^{11}$ or $>C=N-OR^{12}$ where

R^{11} represents a hydrogen atom, a C_1-C_{10} alkanoyl group (preferably an acetyl group), a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least on substituent selected from the group consisting of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one substituent selected from the group consisting of substituents (g), a group of formula $R^{13}-(CH_2)_m-CO-$ where R^{13} and <u>m</u> are as defined above or a group of formula Het-CO- where Het is as defined above, and

R^{12} represents a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_{10} alkyl group having at least one substituent selected from the group consisting of substituents (j), a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one substituent selected from the group consisting of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one substituent selected from the group consisting of substituents (g), or said group of formula $R^{13}-(CH_2)_m-CO-$ or Het-CO-; and

said substituents (j) are selected from the group consisting of hydroxy groups, C_1-C_5 alkoxy groups, phenyl groups, phenyl groups having at least one substituent selected from the group consisting of substituents (g), C_2-C_{11} alkanoyloxy groups, C_2-C_{11} alkanoyloxy groups substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined above, C_3-C_{11} alkenoyloxy groups substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined above, phenylalkenoyloxy groups where the alkenyl part is C_2-C_{10} and the phenyl part is unsubstituted or has at least one substituent selected from the group consisting of substituents (g), benzoyloxy groups, benzoyloxy groups having at least one substituent selected from the group consisting of substituents (g), groups of formula $-COOR^{8a}$ where R^{8a} is as defined above, benzyloxycarbonyl groups and groups of formula $-COR^9R^{10}$ where R^9 and R^{10} are as defined above;

U represents

(i) where W represents a group of formula $-CH_2-$, $>C=O$, $>CH_2OR^{11}$ or $>C=N-OR^{12}$, a group of formula $-CH_2-$,

(ii) with W, a group of formula $-CH=CH-$, or

(iii) where W represents a group of formula $>C=O$ or $>C=N-OR^{14}$, in which R^{14} represents any one of the acyl groups defined for R^{12}, with R^1 and the carbon atom to which R^1 is attached, a group of formula $-CH=C<$. (2) Compounds as defined in (1) above, where:

R^1, R^2, R^4, R^5, Ar, W and U are as defined in (1);

R^6 and R^7 both represent hydrogen atoms;

R^3 and R^{11} are independently selected from the group consisting of hydrogen atoms, C_1-C_{10} alkanoyl groups, C_3-C_{10} alkenoyl groups, C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl groups having at least on substitu nt selected from the group consisting of substituents (f), arylcarbonyl groups as defined in (1) above, and groups of formulae R^{13}-$(CH_2)_m$-CO-and Het-CO-where R^{13}, m and Het are as defined in (1) above; and

R^{12} represents any one of the groups or atoms defined for R^3 and R^{11} or a C_1-C_5 alkyl group or a C_1-C_3 alkyl group having at least one substituent selected from the group consisting of substituents - (f) defined in (1) above.

(3) Compounds as defined in (1) above, where:

R^1, R^2, R^4, R^8, Ar, W and U are as defined in (1);

R^3, R^6, R^7, and R^{12} are independently selected from the group consisting of hydrogen atoms, C_1-C_5 alkyl groups, C_1-C_5 alkyl groups substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in (1) above, C_2-C_5 hydroxyalkyl groups, C_1-C_5 alkyl groups substituted by a C_1-C_5 alkoxy group, C_2-C_5 alkyl groups substituted by a group of formula -O-CO-R^{53} where R^{53} is as defined in (1) above and C_1-C_3 alkyl groups substituted by a single substituent selected from the group consisting of substituents - (h) defined in (1) above; and

R^{11} represents a hydrogen atom, an acetyl group or a benzoyl group;

or

R^{12} represents a hydrogen atom, a C_1-C_5 alkyl group, a C_1-C_{10} alkyl group having at least one substituent selected from the group consisting of substituents (k), a C_2-C_5 alkanoyl group, a C_2-C_{10} alkanoyl group having at least one substituent selected from the group consisting of substituents - (1), a C_3-C_5 alkenoyl group, a C_3-C_5 alkenoyl group having at least one substituent selected from the group consisting of substituents (1), a benzoyl group, a benzoyl group having at least one substituent selected from the group consisting of substituents (m), a pyridinecarbonyl group, a furoyl group, a thenoyl group or a pyridinecarbonyl, furoyl or thenoyl group having at least one substituent selected from the group consisting of C_1-C_5 alkyl groups;

said substituents (k) are selected from the group consisting of hydroxy groups, phenyl groups, phenyl groups having at least one substituent selected from the group consisting of substituents (m), C_2-C_5 alkanoyloxy groups, C_2-C_{10} alkanoyloxy or C_3-C_{10} alkenoyloxy groups substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in (1) abov , C_3-C_{10} alkenoyloxy groups substituted by a phenyl group wher the phenyl group is unsubstituted or has at least one substituent selected from the group consisting of substituents (m), benzoyloxy groups, benzoyloxy groups having at least one substituent selected from the group consisting of substituents (m), groups of formula -$COOR^{8a}$ where R^{8a} is as defined in (1) above and substituents (h) as defined in (1) above;

said substituents (1) are selected from the group consisting of phenyl groups, carboxy groups, alkoxycarbonyl groups where the alkoxy part is C_1-C_5 and benzyloxycarbonyl groups; and

said substituents (m) are selected from the group consisting of C_1-C_5 alkyl groups, C_1-C_5 alkoxy groups, halogen atoms and trifluoromethyl groups.

(4) Compounds of formula (I) in which:

R^1 represents an alkyl group selected from the group consisting of methyl, ethyl, isobutyl, pentyl, hexyl, 3,3-dimethylbutyl, heptyl, 4,4-dimethylpentyl, octyl, 5,5-dimethylhexyl, nonyl and 3,7-dimethyloctyl groups;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one substituent selected from the group consisting of substituents (f) defined in (1) above, a benzoyl group, a benzoyl group having at least one substituent selected from the group consisting of substituents (n), an aralkanoyl group of formula R^{15}-$(CH_2)_m$-CO-

where R^{15} represents a phenyl group or a phenyl group having at least one substituent selected from the group consisting of substituents (n), and m is an integer from 1 to 5,

a pyridinecarbonyl group, a furoyl group, a thenoyl group, a C_1-C_3 alkyl group, a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ wher R^{8a} is as defined in (1) above, a C_2-C_3 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group or a methyl group having a singl substituent selected from the group consisting of substituents (h);

said substituents (n) are selected from the group

consisting of C_1-C_5 alkyl groups, C_1-C_5 alkoxy groups and halogen atoms;

R^4 represents a C_1-C_{10} alkyl group;

R^5 represents a hydrogen atom or a C_1-C_3 alkyl group;

R^6 and R^7 are independently selected from the group consisting of hydrogen atoms, C_1-C_3 alkyl groups, C_1-C_3 alkyl groups substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above, C_2-C_3 hydroxyalkyl groups, C_1-C_5 alkyl groups substituted by a C_1-C_5 alkoxy group, C_2-C_5 alkyl groups substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group, and methyl groups substituted by a single substituent selected from the group consisting of substituents (h);

Ar represents a o-phenylene, m -phenylene or p-phenylene group or a pyridine-diyl group which is attached to the part of said compound of formula -(I) of formula $-(CH_2)_n$-O-at its 2-position and is attached to the $-CH_2$-thiazolidine group at its 5-or 6-position, said phenylene and pyridine-diyl groups being unsubstituted or having a methyl substituent;

W represents a group of formula $-CH_2-$, >C = O, >CH-OR^{11} or >C = N-OR^{12}, where:

R^{11} represents a hydrogen atom or any one of the acyl groups defined above for R^3; and

R^{12} represents a benzyl group, any one of the groups or atoms defined above for R^3, a pyridinecarbonyl group or a pyridinecarbonyl group having at least one substituent selected from the group consisting of C_1-C_5 alkyl groups;

and U represents

(i) where W represents a group of formula -CH_2-, >C = O, >CH-OR^{11} or >C = N-OR^{12}, a group of formula $-CH_2-$,

(ii) with W, a group of formula -CH = CH-, or

(iii) where W represents a group of formula > C = O, with R^1 and the carbon atom to which R^1 is attached, a group of formula -CH = C<. (5) Compounds as defined in (4) above, where:

R^1, R^2, R^4, R^5, Ar, W and U are as defined in (4) above;

R^6 and R^7 are both hydrogen atoms;

R^3 and R^{11} ar independently selected from the group consisting of hydrogen atoms, C_1-C_{10} alkanoyl groups, C_3-C_{10} alkenoyl groups, C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl groups having at least one substituent selected from the group consisting of substituents (f) defined above, benzoyl groups, benzoyl groups having at least one substituent selected from the group consisting of substituents -(n) defined in (4) above, groups of formula R^{15}-$(CH_2)_m$-CO-where R^{15} and m are as defined in (4) above, pyridinecarbonyl groups, furoyl groups and thenoyl groups; and

R^{12} represents a hydrogen atom, a methyl group, a benzyl group, a t-butoxycarbonylmethyl group or any one of the acyl groups defined above for R^3 and R^{11}.

(6) Compounds as defined in (4) above, where:

R^1, R^2, R^4, R^5, Ar, W and U are as defined in (4) above;

R^3,R^6 and R^7 are independently selected from the group consisting of C_1-C_3 alkyl groups, C_1-C_3 alkyl groups substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above, C_2-C_3 hydroxyalkyl groups, C_1-C_5 alkyl groups substituted by a C_1-C_5 alkoxy group, C_2-C_5 alkyl groups substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group, and methyl groups having a single substituent selected from the group consisting of substituents (h) defined in (1) above;

R^{11} represents a hydrogen atom;

R^{12} represents a hydrogen atom, a C_1-C_3 alkyl group having at least one substituent selected from the group consisting of substituents (o), a C_2-C_4 alkanoyl group, a C_2-C_4 alkanoyl group substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above, an acryloyl group, an acryloyl group having a β-substituent selected from the group consisting of substituents (f) defined above, a benzoyl group, a benzoyl group having at least one substituent selected from the group consisting of substituents (q), a pyridinecarbonyl group, a pyridinecarbonyl group having at least one substituent selected from the group consisting of C_1-C_5 alkyl groups or any one of the groups defined above for R^3, R^6 and R^7;

said substituents (o) are selected from the group consisting of carboxy groups and alkoxycarbonyl groups where the alkoxy part is C_1-C_5; and

said substituents (q) are selected from the group consisting of methyl groups, ethyl groups, methoxy groups and ethoxy groups.

(7) Compounds of formula (I) in which:

R^1 r presents an alkyl group selected from the group consisting of methyl, isobutyl, hexyl, heptyl, octyl, nonyl and 3,7-dimethyloctyl groups;

R^2 r pres nts a hydrogen atom r a methyl group;

R^3 represents a hydrogen atom, a C_1-C_6 alkanoyl group, C_3-C_6 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-

where R^{16} represents a hydrogen atom or a C_1-C_6 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula $R^{17}OOC.CH=CH$-CO-

where R^{17} represents a hydrogen atom, a C_1-C_5 alkyl group or a benzyl group,

a 2-, 3-or 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above;

R^4 represents an alkyl group selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl and 1,1-dimethylpropyl groups;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are independently selected from the group consisting of hydrogen atoms and C_1-C_3 alkyl groups substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula $-(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula $-(CH_2)_n$-O-at the 2-position and to the $-CH_2$-thiazolidine group at the 5-position;

W represents a group of formula $-CH_2$-, >C=O, >C=N-OH, >C=N-OCH_2COOH or >C=N-$OCOR^{18}$

where R^{18} represents a C_1-C_6 alkyl group; and

U represents a group of formula $-CH_2$-.

(7-a) Compounds of formula (I) in which:

R^1 represents an alkyl group selected from the group consisting of hexyl, heptyl, octyl, nonyl and 3,7-dimethyloctyl groups;

R^2 r presents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_6 alkanoyl group, C_3-C_6 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-

where R^{16} represents a hydrogen atom or a C_1-C_6 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula $R^{17}OOC.CH=CH$-CO-

where R^{17} represents a hydrogen atom, C_1-C_5 alkyl group or a benzyl group,

a 2-, 3-or 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above;

R^4 represents an alkyl group selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl and 1,1-dimethylpropyl groups;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are independently selected from the group consisting of hydrogen atoms and C_1-C_3 alkyl groups substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above;

Ar represents a p -phenylene group, am-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula $-(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula $-(CH_2)_n$-O-at the 2-position and to the $-CH_2$-thiazolidine group at the 5-position;

W represents a group of formula $-CH_2$-, >C=O or >C=N-OR^{12}

where R^{12} is as defined in (9) below or represents a C_1-C_6 alkyl group or a C_1-C_6 alkyl group substituted by a phenyl group where the phenyl group is unsubstituted or has at least one substituent selected from the group consisting of substituents - (n) as defined in (4) above; and

U represents a group of formula $-CH_2$-.

(7-b) Compounds of formula (I) in which:

R^1 represents an alkyl group selected from the group consisting of methyl, isobutyl, hexyl, heptyl, octyl, nonyl and 3,7-dimethyloctyl groups;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_6 alkanoyl group, C_3-C_6 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-

wher R^{16} represents a hydrogen atom or a C_1-C_5 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula $R^{17}OOC.CH = CH$-CO-

where R^{17} represents a hydrogen atom, a C_1-C_5 alkyl group or a benzyl group,

a 2-, 3-or 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above;

R^4 represents an alkyl group selected from the group consisting of hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl and 1,1-dimethylpropyl groups;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are independently selected from the group consisting of hydrogen atoms and C_1-C_3 alkyl groups substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in (1) above;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula $-(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula $-(CH_2)_n$ -O-at the 2-position and to the $-CH_2$-thiazolidine group at the 5-position;

W represents a group of formula $-CH_2$-, >C=O or >C=N-OR^{12}

where R^{12} is as defined in (9) below or represents a C_1-C_6 alkyl group or a C_1-C_6 alkyl group substituted by a phenyl group where the phenyl group is unsubstituted or has at least one substituent selected from the group consisting of substituents - (n) as defined in (4) above; and

U represents a group of formula $-CH_2$-.

(7-c) Compounds of formula (I) in which:

R^1 represents an alkyl group selected from the group consisting of methyl, isobutyl, hexyl, heptyl, octyl, nonyl and 3,7-dimethyloctyl groups;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents C_1-C_3 alkyl group substituted by a group of formula $-COOR^{8a}$

where R^{8a} is as defined in (1) above;

R^4 represents an alkyl group selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl and 1,1-dimethylpropyl groups;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are both hydrogen atoms;

Ar represents a p-phenylene group, a m -phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula $-(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula $-(CH_2)_n$ -O-at the 2-position and to the $-CH_2$-thiazolidine group at the 5-position;

W represents a group of formula $-CH_2$-, >C=O, >C=N-OH, or > C=N-O-(C_1-C_3 alkyl)-$COOR^{8a}$ where R^{8a} is as defined in (1) above;

U represents a group of formula $-CH_2$-; and

n is 1 or 2.

(7-d) Compounds of formula (I) in which:

R^1 represents an alkyl group selected from the group consisting of methyl, isobutyl, hexyl, heptyl, octyl, nonyl and 3,7-dimethyloctyl groups;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents group of formula $-CH_2-COOR^{8a}$ where R^{8a} is as defined in (1) above;

R^4 represents an alkyl group selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl and 1,1-dimethylpropyl groups;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are both hydrogen atoms;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula $-(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula $-(CH_2)_n$-O-at the 2-position and to the $-CH_2$-thiazolidine group at the 5-position;

W represents a group of formula $-CH_2$-, >C=O, >C=N-OH, or >C=N-O-(C_1-C_3 alkyl)-$COOR^{8a}$ where R^{8a} is as defined in (1) above;

U represents a group of formula $-CH_2$-; and

n is 1 or 2.

(8) Compounds as defined in (7) above, where:

R^1, R^2, R^4, R^5, Ar and U are as defined in (7) above;

R^3 represents a hydrogen atom, a C_1-C_5 alkanoyl group, a C_3-C_5 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-where R^{16} and m are as defined in (7) above, a cis or trans-group of formula $R^{17}OOC.CH=CH$-CO-where R^{17} is as defined in (7) above, or a 2-, 3-or 4-pyridinecarbonyl group;

R^6 and R^7 are both hydrogen atoms;

W represents a group of formula >C=NOR^{12} where R^{12} is as defined in (9) below; and

n is 1 or 2.

(9) Compounds as defined in (7) above, where:

R^1, R^2, R^4, R^5, Ar and U are as defined in (7) above;

R^3, R^6 and R^7 are independently selected from the group consisting of C_1-C_3 alkyl groups substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in (1) above;

W represents a group of formula >CH$_2$, >C=O or >C=NOR^{12};

R^{12} represents a hydrogen atom, a group of formula -$(CH_2)_3COOR^{8a}$, -CH_2COOR^{8a}, -$C(CH_3)_2COOR^{8a}$, -$COCH_2CH_2COOR^{8a}$ or -CO-CH=CH-COOR^{8a} where R^{8a} is as defined in (1) above, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group or any one of the groups defined above for R^3, R^6, and R^7; and

n is 1 or 2.

(9-a) Compounds as defined in (7) above, where:

R^1, R^2, R^4, R^5, Ar and U are as defined in (7) above;

R^3 represents a hydrogen atom, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alk noyl group, a C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one substituent selected from the group consisting of substituents (f), an arylcarbonyl group as defined in - (1) above, a group of formula R^{13}-$(CH_2)_m$-CO-or Het-CO-where R^{13}, m and Het are as defined in (1) above or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in (1) above;

R^6 represents a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in (1) above;

R^7 represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in (1) above;

W represents a group of formula >CH$_2$, >C=O or >C=NOR^{12}, where

R^{12} represents a hydrogen atom, a group of formula -$(CH_2)_3COOR^{8a}$, -CH_2COOR^{8a}, -$C(CH_3)_2COOR^{8a}$, -$COCH_2CH_2COOR^{8a}$ or -CO-CH=CH-COOR^{8a} where R^{8a} is as defined in (1) above, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in (1) above; and

n is 1 or 2.

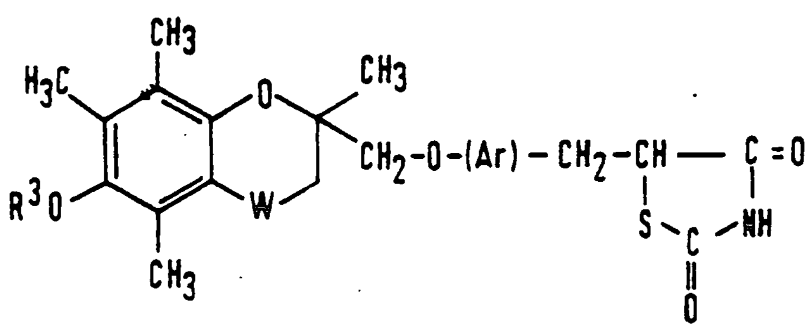
Specific examples of compounds of the invention are given in the following Tables 1-26, referring to the formulae (I-1) to (I-26). In the Tables, the following abbreviations are used:

Ac	acetyl
Boz	benzoyl
Bu	butyl
iBu	isobutyl
tBu	t-butyl
Bz	benzyl
Dc	decyl
3,3-DMB	3,3-dimethylbutyl
5,5-DMH	5,5-dimethylhexyl
3,7-DMO	3,7-dimethyloctyl
7,7-DMO	7,7-dimethyloctyl
Et	ethyl
Hp	heptyl
Hx	hexyl
Hxd	hexadecyl
Ic	icosyl
Me	methyl
Mor	morpholino
Nn	nonyl
Oc	octyl

Ocd	octadecyl
Ph	phenyl
Phn	phenylene
Pip	piperidino
Piz	piperazinyl
Pn	pentyl
<u>i</u>Pn	isopentyl
<u>n</u>Pn	neopentyl
Pr	propyl
<u>i</u>Pr	isopropyl
Pydi	pyridine-diyl
Pyl	pyrrolidinyl
Pyr	pyridyl
TMB	1,1,3,3-tetramethylbutyl
Trd	tridecyl

In the case of the divalent group represented by Ar, where appropriate, the number given first is the position of attachment of that group to the group represented by $-(CH_2)_n-O-$in the compound of formula (I), whilst the number given second is the position of attachment of that group to the $-CH_2$-thiazolidine group.

Compounds of formula (I-1):



(I-1)

are as defined in Table 1:

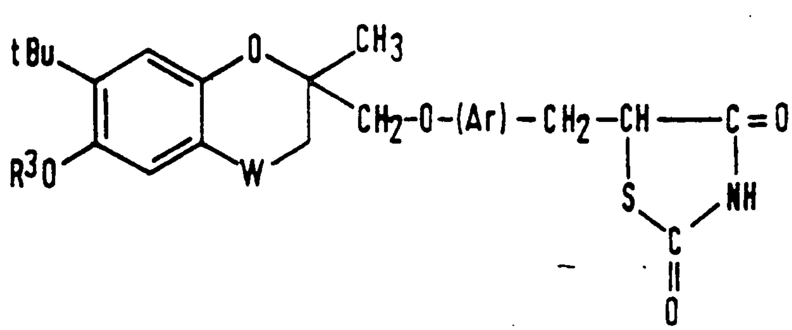
Table 1

Cpd. No.	R^3	W	Ar
1	H	>CH_2	6-Me-1,3-Phn
2	Ac	>CH_2	6-Me-1,3-Phn
3	H	>C=O	6-Me-1,3-Phn
4	H	>C=NOH	6-Me-1,3-Phn
5	H	>CH_2	2,5-Pydi
6	H	>C=O	2,5-Pydi
7	Ac	>C=O	2,5-Pydi
8	H	>C=NOH	2,5-Pydi
9	H	>C=NOH (anti)	p-Phn
10	H	>C=NOH (syn)	p-Phn
11	Ac	>C=NOAc	p-Phn
12	Boz	>C=NOBoz	p-Phn
13	3-PyrCO	>C=NO(3-PyrCO)	p-Phn

Table 1 (cont)

Cpd. No.	R^3	W	Ar
14	H	>C=NOMe	p-Phn
15	H	>C=NOBz	p-Phn
16	H	>C=NO(4-MeBz)	p-Phn
17	H	>C=NOCH$_2$COOH	p-Phn
18	Ac	>C=NOCH$_2$COOMe	p-Phn
19	H	>C=NOCH$_2$COOEt	p-Phn
20	H	>C=NOCH$_2$COO<u>i</u>Pr	p-Phn
21	H	>C=NOCH$_2$COO<u>t</u>Bu	p-Phn
22	Me(CH$_2$)$_{14}$CO-	>CH$_2$	p-Phn
23	HOOC(CH$_2$)$_2$CO-	>CH$_2$	p-Phn
24	HOOCCH=CHCO-(cis)	>CH$_2$	p-Phn
25	HOOC(CH$_2$)$_2$CO-	>C=O	p-Phn
26	HOOC(CH$_2$)$_3$CO-	>CH-OH	p-Phn
27	HOOC(CH$_2$)$_2$CO-	>C=NOH	p-Phn
28	HOOC(CH$_2$)$_2$CO-	>CH$_2$	2,5-Pydi
29	HOOC(CH$_2$)$_2$CO-	>C=NOCH$_2$COOH	p-Phn
30	HOOC(CH$_2$)$_2$CO-	>C=NOCH$_2$COOH	2,5-Pydi

Compounds of formula (I-2):



(I-2)

are as defined in Table 2:

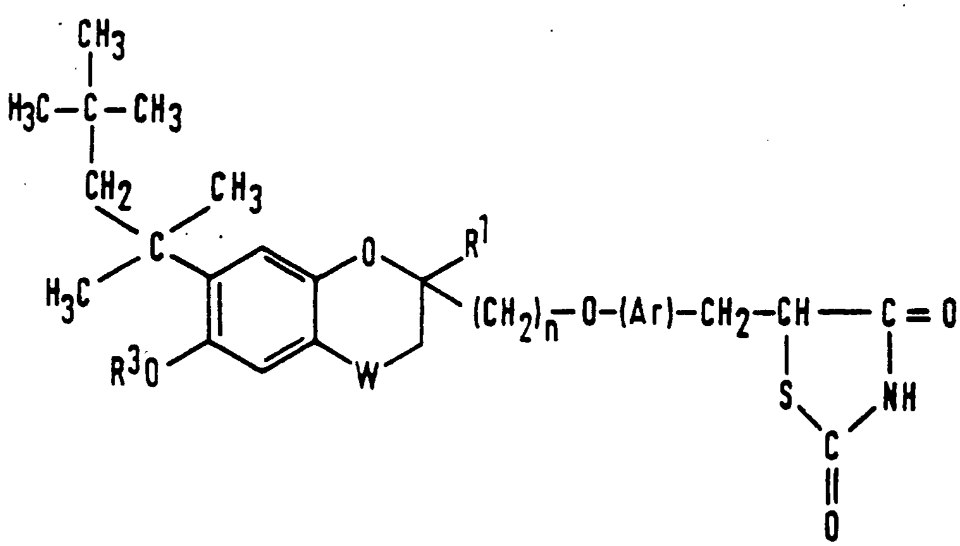
Table 2

Cpd. No.	R^3	W	Ar
31	H	$>CH_2$	6-Me-1,3-Phn
32	H	>C=O	6-Me-1,3-Phn
33	H	>C=NOH	6-Me-1,3-Phn
34	H	$>CH_2$	2,5-Pydi
35	Ac	$>CH_2$	2,5-Pydi
36	H	>C=O	2,5-Pydi
37	Ac	>C=O	2,5-Pydi
38	H	>C=NOH	2,5-Pydi
39	H	>C=NOH (anti)	p-Phn
40	Ac	>C=NOAc	p-Phn

Table 2 (cont)

Cpd. No.	R^3	W	Ar
41	Boz	>C=NOBoz	p-Phn
42	3-PyrCO	>C=NO(3-PyrCO)	p-Phn
43	H	>C=NOMe	p-Phn
44	H	>C=NOBz	p-Phn
45	H	>C=NO(2-OMeBz)	p-Phn
46	H	>C=NOCH$_2$COOH	p-Phn
47	H	>C=NOCH$_2$COOEt	p-Phn
48	H	>C=NOCH$_2$COOiPr	p-Phn
49	H	>C=NOCH$_2$COOtBu	p-Phn
50	HOOC(CH$_2$)$_6$CO-	>CH$_2$	m-Phn

Compounds of formula (I-3):



(I-3)

are as defined in Table 3:

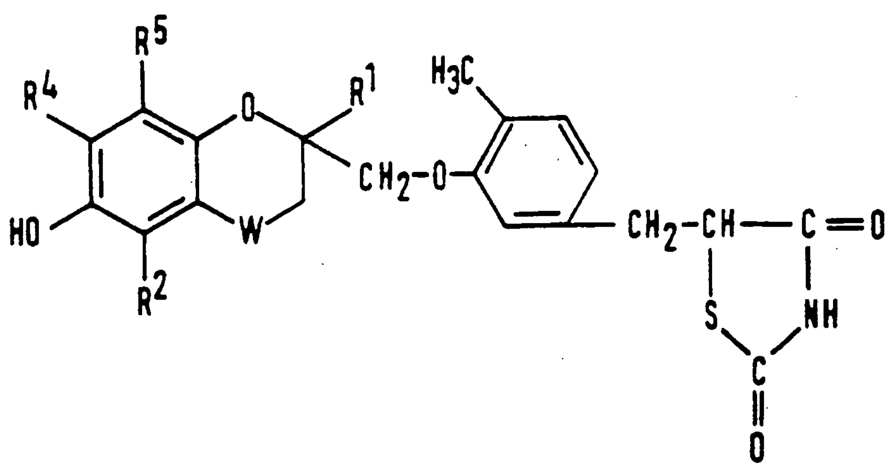
Table 3

Cpd. No.	R^1	R^3	n	W	Ar
51	Me	H	1	$>CH_2$	p-Phn
52	Me	H	1	>C=O	p-Phn
53	Me	H	1	>C=NOH	p-Phn
54	Me	H	2	$>CH_2$	p-Phn
55	Me	H	1	$>CH_2$	6-Me-1,3-Phn
56	Me	Ac	1	$>CH_2$	p-Phn
57	Me	Ac	1	>C=O	p-Phn
58	Me	H	1	>C=NOH	6-Me-1,3-Phn
59	Me	H	2	$>CH_2$	6-Me-1,3-Phn
60	Me	H	1	$>CH_2$	2,5-Pydi
61	Me	H	1	>C=O	2,5-Pydi
62	Me	H	1	>C=NOH	2,5-Pydi
63	iPr	H	1	>C=O	p-Phn
64	Bz	H	1	$>CH_2$	p-Phn
65	Bz	H	1	>C=NOH	p-Phn
66	Bz	H	1	>C=NOH	2,5-Pydi
67	Hx	H	1	$>CH_2$	p-Phn
68	Hx	H	1	>C=O	p-Phn
69	Hx	H	1	>C=NOH	p-Phn
70	Hx	H	1	$>CH_2$	2,5-Pydi
71	3,3-DMB	H	1	$>CH_2$	p-Phn
72	Hp	H	1	$>CH_2$	p-Phn

Table 3 (cont)

Cpd. No.	R^1	R^3	n	W	Ar
73	Oc	H	1	$>CH_2$	p-Phn
74	Oc	H	1	>C=O	p-Phn
75	Oc	H	1	>C=NOH	p-Phn
76	Oc	H	1	$>CH_2$	2,5-Pydi
77	5,5-DMH	H	1	$>CH_2$	p-Phn
78	5,5-DMH	H	1	>C=O	p-Phn
79	5,5-DMH	H	1	>C=NOH	p-Phn
80	Dc	H	1	$>CH_2$	p-Phn
81	Me	HOOCCH=CHCO- (trans)	1	$>CH_2$	p-Phn

Compounds of formula (I-4):



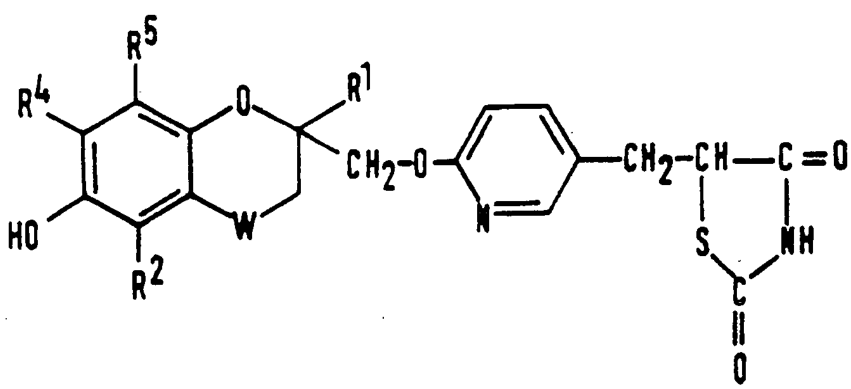
(I-4)

are as defined in Table 4:

Table 4

Cpd. No.	R^1	R^2	R^4	R^5	W
82	Me	iPr	iPr	Me	>C=NOH
83	Et	Me	Me	Me	$>CH_2$
84	Et	H	tBu	H	$>CH_2$
85	Pr	Me	Me	Me	$>CH_2$
86	iBu	Me	Me	Me	$>CH_2$
87	Bz	Me	Me	Me	$>CH_2$
88	1-MeHx	H	tBu	H	>C=NOH
89	Oc	Me	Me	Me	$>CH_2$
90	Oc	Me	Me	Me	>C=O
91	Oc	Me	Me	Me	>C=NOH
92	Oc	H	tBu	H	$>CH_2$
93	5,5-DMH	Me	Me	Me	$>CH_2$
94	Dc	Me	Me	Me	>C=O

Compounds of formula (I-5):



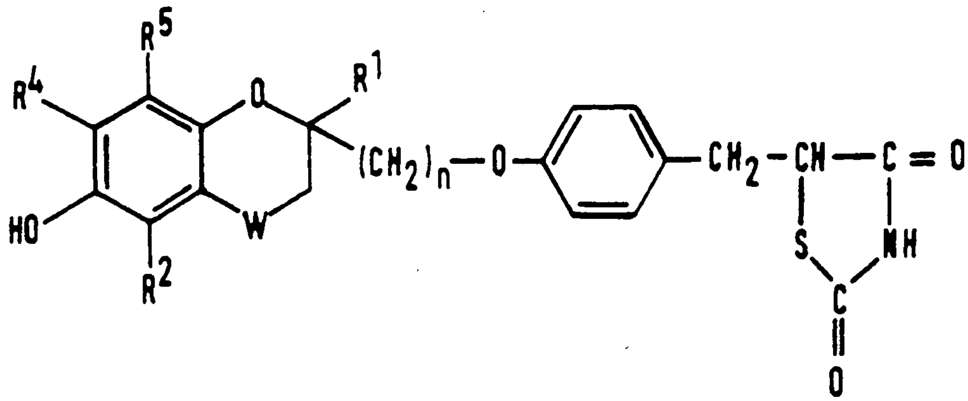
(I-5)

are as defined in Table 5:

Table 5

Cpd. No.	R^1	R^2	R^4	R^5	W
95	Et	iPr	iPr	H	>C=O
96	Bz	Me	Me	Me	>CH_2
97	Bz	Me	Me	Me	>C=NOH
98	2-OMeBz	H	tBu	H	>C=NOH
99	Hx	Me	Me	Me	>CH_2
100	Hx	Me	Me	Me	>C=O
101	Hx	Me	Me	Me	>C=NOH
102	Hx	H	tBu	H	>CH_2
103	Hx	H	tBu	H	>C=O
104	Hx	H	tBu	H	>C=NOH
105	3,3-DMB	H	tBu	H	>CH_2
106	Hp	Me	Me	Me	>CH_2
107	Hp	H	tBu	H	>CH_2
108	Oc	Me	Me	Me	>CH_2
109	Oc	Me	Me	Me	>C=O
110	Oc	Me	Me	Me	>C=NOH
111	5,5-DMH	Me	Me	Me	>CH_2
112	5,5-DMH	Me	Me	Me	>C=NOH
113	5,5-DMH	H	tBu	H	>CH_2
114	Dc	Me	Me	Me	>C=NOH

Compounds of formula (I-6):



(I-6)

are as defined in Table 6:

Table 6

Cpd. No.	R^1	R^2	R^4	R^5	W	n
115	iPr	H	tBu	H	>C=NOH	1
116	Bz	Me	Me	Me	$>CH_2$	1
117	Bz	Me	Me	Me	>C=O	1
118	iBu	Me	Me	Me	>C=NOH	1
119	Bz	H	tBu	H	$>CH_2$	1
120	4-MeBz	H	Me	H	>CH-OH	1
121	3-ClBz	iPr	iPr	H	>C=NOH	1
122	2-PhEt	Me	Me	Me	$>CH_2$	2
123	Hx	Me	Me	Me	$>CH_2$	1
124	Hx	Me	Me	Me	>C=O	1

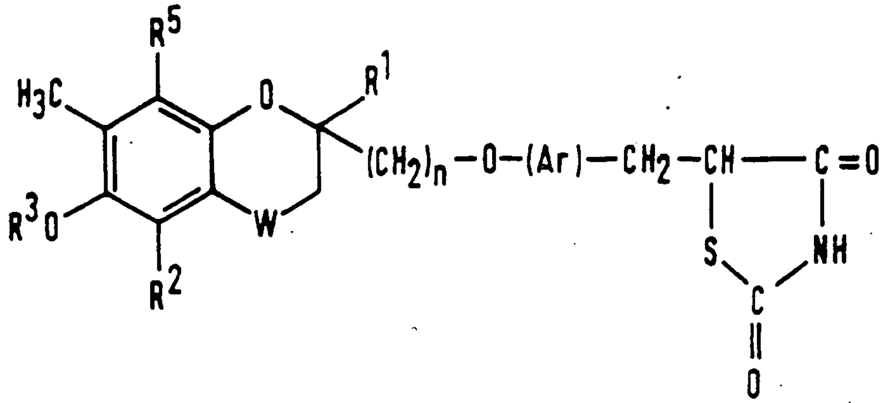
Table 6 (cont)

Cpd. No.	R^1	R^2	R^4	R^5	W	n
125	Hx	Me	Me	Me	>C=NOH	1
126	Hx	H	tBu	H	>CH_2	1
127	Hx	H	tBu	H	>C=O	1
128	Hx	H	tBu	H	>C=NOH	1
129	1-MePn	Me	Me	Me	>CH_2	1
130	3,3-DMB	Me	Me	Me	>CH_2	1
131	3,3-DMB	Me	Me	Me	>C=O	1
132	3,3-DMB	Me	Me	Me	>C=NOH	1
133	3,3-DMB	H	tBu	H	>CH_2	1
134	1-EtBu	Me	Me	Me	>CH_2	2
135	3-MePn	iPr	iPr	H	>CH-OH	1
136	Hp	Me	Me	Me	>CH_2	1
137	Hp	Me	Me	Me	>C=O	1
138	Hp	Me	Me	Me	>C=NOH	1
139	Hp	H	tBu	H	>CH_2	1
140	Hp	H	tBu	H	>C=O	1
141	4,4-diMePn	Me	Me	Me	>CH_2	1
142	Oc	Me	Me	Me	>CH_2	1
143	Oc	Me	Me	Me	>C=O	1
144	Oc	Me	Me	Me	>C=NOH	1
145	Oc	H	tBu	H	>CH_2	1
146	Oc	H	tBu	H	>C=O	1

Table 6 (cont)

Cpd. No.	R^1	R^2	R^4	R^5	W	n
147	Oc	H	tBu	H	>C=NOH	1
148	5,5-DMH	Me	Me	Me	>CH_2	1
149	5,5-DMH	Me	Me	Me	>C=O	1
150	5,5-DMH	Me	Me	Me	>C=NOH	1
151	5,5-DMH	H	tBu	H	>CH_2	1
152	5,5-DMH	H	tBu	H	>C=O	1
153	5,5-DMH	H	tBu	H	>C=NOH	1
154	Nn	Me	Me	Me	>CH_2	1
155	Dc	Me	Me	Me	>CH_2	1
156	Dc	H	tBu	H	>CH_2	1
157	1-MeNn	Me	Me	H	>CH_2	1
158	3,7-DMO	Me	Me	Me	>CH_2	1
159	3,7-DMO	Me	Me	Me	>C=O	1
160	3,7-DMO	Me	Me	Me	>C=NOH	1
161	3,7-DMO	H	tBu	H	>CH_2	1
162	3,7-DMO	H	tBu	H	>C=O	1
163	7,7-DMO	Me	Me	Me	>CH_2	1
164	7,7-DMO	Me	Me	Me	>C=O	1

Compounds of formula (I-7):



(I-7)

are as defined in Table 7:

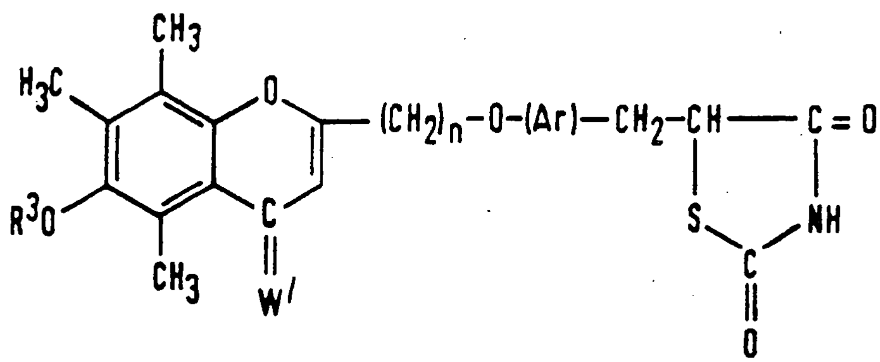
Table 7

Cpd. No.	R^1	R^2	R^3	R^5
165	2-(3-OEtPh)Et	H	H	H
166	Hx	Me	H	H
167	Oc	Me	Ac	Me
168	Oc	Me	Ac	Me
169	5,5-DMH	Me	Ac	Me
170	3,7-DMO	Me	Ac	Me
171	7,7-DMO	Me	Ac	Me
172	Pr	Me	$EtOOC(CH_2)_2CO-$	Me
173	Oc	Me	$HOOC(CH_2)_4CO-$	Me

Table 7 (cont)

Cpd. No.	W	Ar	n
165	>C=O	2-Me-1,4-Phn	1
166	>CHOH	3-Me-1,4-Phn	1
167	$>CH_2$	p-Phn	1
168	>C=O	p-Phn	1
169	$>CH_2$	2,5-Pydi	1
170	>C=O	p-Phn	1
171	>C=O	p-Phn	1
172	$>CH_2$	p-Phn	1
173	$>CH_2$	p-Phn	2

Compounds of formula (I-8):



(I-8)

are as defined in Table 8:

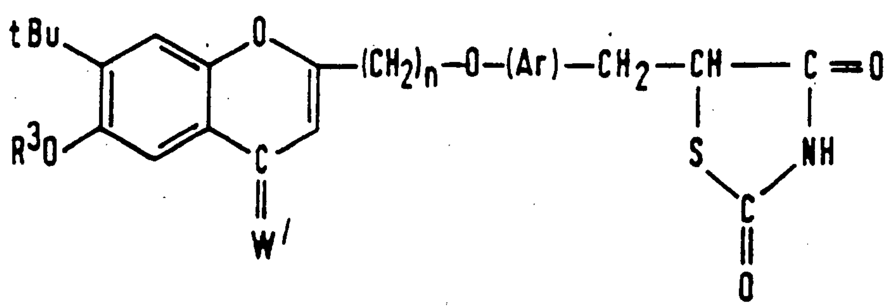
Table 8

Cpd. No.	R^3	W'	Ar	n
174	H	O	p-Phn	1
175	Ac	O	p-Phn	1
176	H	O	p-Phn	2
177	Ac	O	p-Phn	2
178	H	O	p-Phn	3
179	Ac	O	p-Phn	3
180	Boz	O	p-Phn	1
181	H	NOH	p-Phn	1
182	Ac	NOAc	p-Phn	1
183	H	NOH	p-Phn	2
184	H	NOH	p-Phn	3
185	H	O	6-Me-1,3-Phn	1
186	Ac	O	6-Me-1,3-Phn	1
187	H	O	6-Me-1,3-Phn	2
188	H	NOH	6-Me-1,3-Phn	1
189	Ac	NOAc	6-Me-1,3-Phn	1
190	H	O	2,5-Pydi	1
191	Ac	O	2,5-Pydi	1
192	H	O	2,5-Pydi	2
193	H	NOH	2,5-Pydi	1

Table 8 (cont)

Cpd. No.	R^3	W'	Ar	n
194	$HOOC(CH_2)_2CO-$	O	p-Phn	1
195	HOOCCH=CHCO-(cis)	O	p-Phn	1
196	HOOCCH=CHCO-(trans)	O	2,5-Pydi	1
197	$HOOC(CH_2)_2CO-$	O	p-Phn	2
198	$HOOC(CH_2)_2CO-$	NOH	p-Phn	1
199	$HOOC(CH_2)_2CO-$	$NOCH_2COOH$	p-Phn	1
200	$HOOC(CH_2)_2CO-$	$NOCH_2COOH$	2,5-Pydi	1
201	$HOOC(CH_2)_2CO-$	$NOCH_2COO\underline{t}Bu$	p-Phn	1
202	$EtOOC(CH_2)_6CO-$	$NOCH_2COOEt$	p-Phn	1

Compounds of formula (I-9):



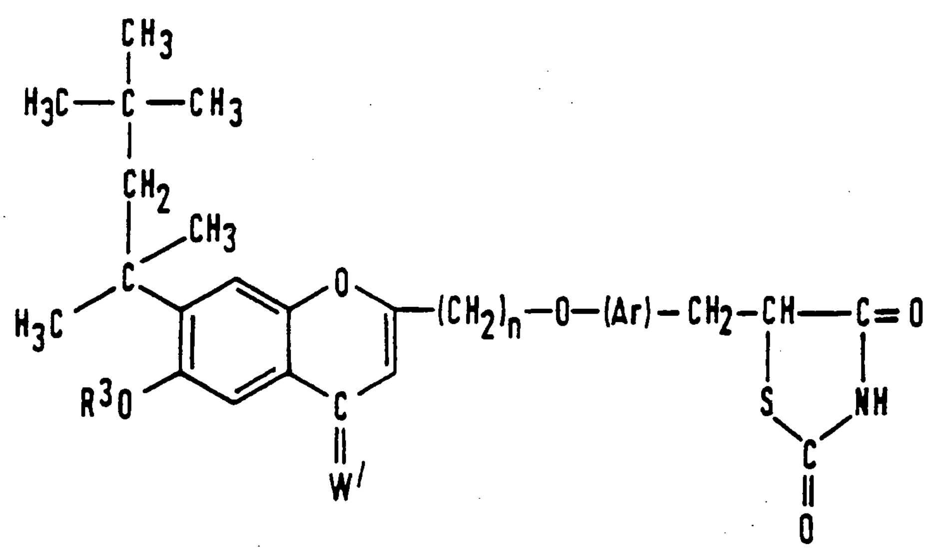
(I-9)

are as defined in Table 9:

Table 9

Cpd. No.	R^3	W'	Ar	n
203	H	O	p-Phn	1
204	Ac	O	p-Phn	1
205	H	O	p-Phn	2
206	Ac	O	p-Phn	2
207	H	NOH	p-Phn	1
208	H	O	6-Me-1,3-Phn	1
209	Ac	O	6-Me-1,3-Phn	1
210	H	O	2,5-Pydi	1
211	Ac	O	2,5-Pydi	1
212	Ac	NOH	2,5-Pydi	1
213	$HOOC(CH_2)_2CO-$	O	p-Phn	1

Compounds of formula (I-10):



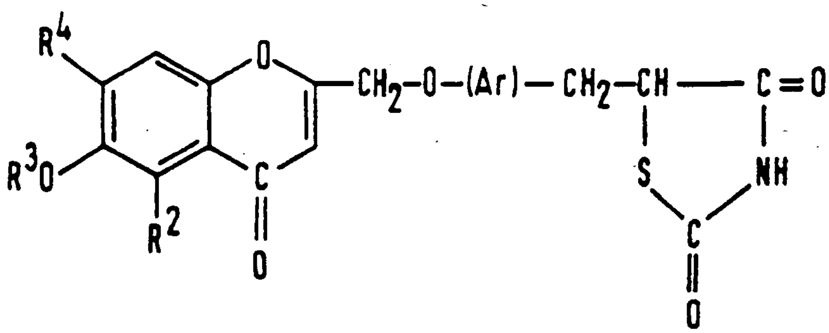
(I–10)

are as defined in Table 10:

Table 10

Cpd. No.	R^3	W'	Ar	n
214	H	O	p-Phn	1
215	Ac	O	p-Phn	1
216	Ac	NOH	p-Phn	1
217	H	NOH	p-Phn	2
218	H	O	6-Me-1,3-Phn	1
219	Ac	O	6-Me-1,3-Phn	1
220	H	O	6-Me-1,3-Phn	2
221	H	NOH	6-Me-1,3-Phn	1
222	H	O	2,5-Pydi	1
223	$HOOC(CH_2)_2CO-$	O	p-Phn	1
224	$HOOC(CH_2)_2CO-$	$NOCH_2COOH$	2,5-Pydi	1

Compounds of formula (I-11):



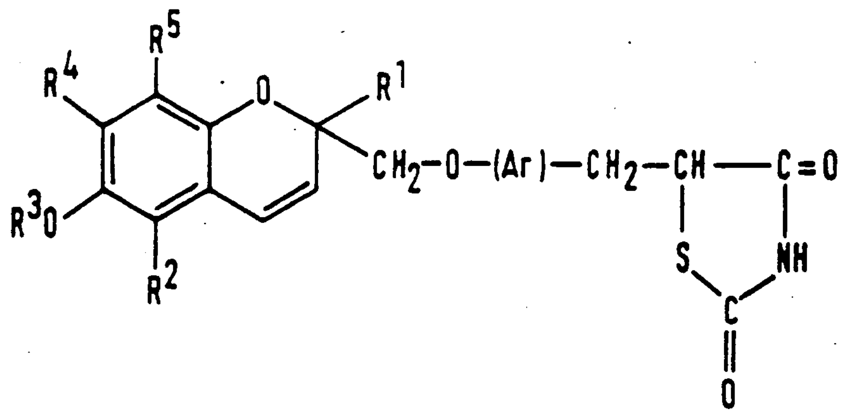
(I-11)

are as defined in Table 11:

Table 11

Cpd. No.	R^2	R^3	R^4	Ar
225	iPr	H	iPr	p-Phn
226	Me	$EtOOC(CH_2)_4CO-$	Me	6-Me-1,3-Phn

Compounds of formula (I-12):



(I-12)

are as defined in Table 12:

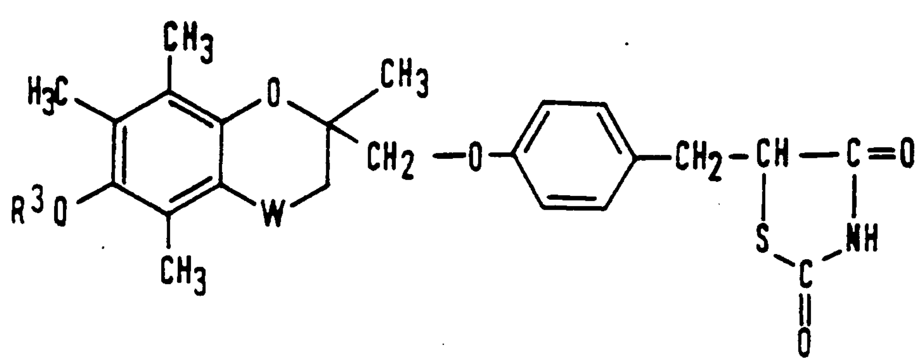
Table 12

Cpd. No.	R^1	R^2	R^3	R^4	R^5	Ar
227	Me	Me	H	Me	Me	p-Phn
228	Me	Me	Ac	Me	Me	p-Phn
229	Me	Me	Boz	Me	Me	p-Phn
230	Me	Me	H	Me	Me	6-Me-1,3-Phn
231	Me	Me	Ac	Me	Me	6-Me-1,3-Phn
232	Me	Me	H	Me	Me	2,5-Pydi
233	Me	Me	Ac	Me	Me	2,5-Pydi
234	Me	H	H	tBu	H	p-Phn
235	Me	H	Ac	tBu	H	p-Phn
236	Me	H	H	tBu	H	6-Me-1,3-Phn
237	Me	H	Ac	tBu	H	6-Me-1,3-Phn
238	Me	H	H	tBu	H	2,5-Pydi
239	Me	H	Ac	tBu	H	2,5-Pydi
240	Me	iPr	H	iPr	H	p-Phn
241	Me	H	H	TMB	H	p-Phn
242	Me	H	H	TMB	H	6-Me-1,3-Phn
243	Me	H	H	TMB	H	2,5-Pydi
244	Et	Me	H	Me	Me	p-Phn
245	Pr	H	H	tBu	H	p-Phn
246	Pr	H	Ac	tBu	H	p-Phn
247	iPr	H	H	TMB	H	p-Phn
248	iBu	Me	H	Me	Me	p-Phn

Table 12 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	Ar
249	iBu	Me	Ac	Me	Me	p-Phn
250	Bu	H	H	tBu	H	p-Phn
251	iBu	H	H	TMB	H	p-Phn
252	nPn	Me	H	Me	Me	p-Phn
253	iPn	H	H	tBu	H	p-Phn
254	Pn	H	H	TMB	H	2,5-Pydi
255	Hx	Me	H	Me	Me	p-Phn
256	Oc	Me	H	Me	Me	p-Phn
257	Dc	Me	H	Me	Me	p-Phn
258	3,7-DMO	H	H	tBu	H	p-Phn
259	7,7-DMO	H	H	tBu	H	6-Me-1,3-Phn
260	3,7-DMO	H	H	tBu	H	2,5-Pydi
261	7,7-DMO	H	H	TMB	H	p-Phn
262	Bz	H	H	TMB	H	p-Phn
263	Me	Me	$HOOC(CH_2)_2CO-$	Me	Me	p-Phn
264	Me	H	$HOOC(CH_2)_2CO-$	tBu	H	p-Phn
265	Me	H	$HOOC(CH_2)_2CO-$	TMB	H	p-Phn

Compounds of formula (I-13):



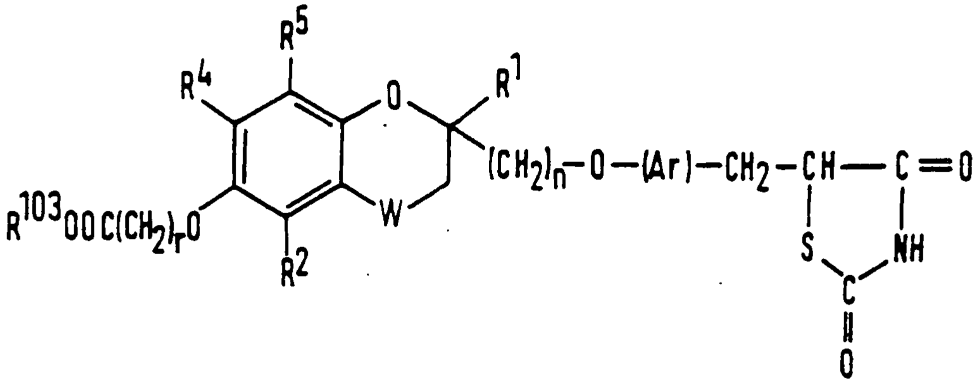
(I-13)

are as defined in Table 13:

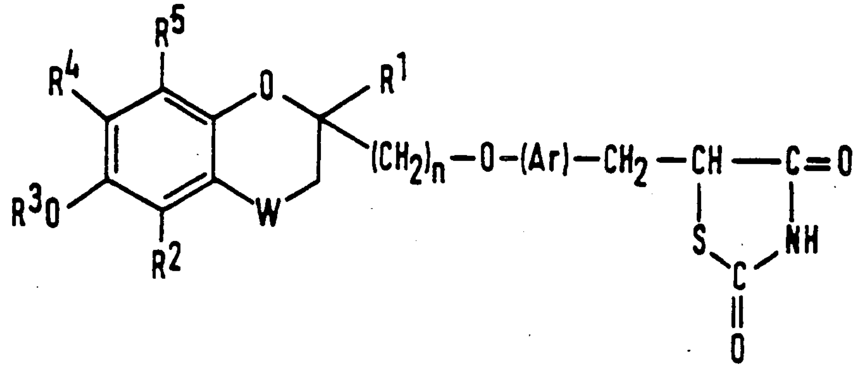
Table 13

Cpd. No.	R^3	W
266	Et	$>CH_2$
267	<u>i</u>Pr	>C=NOH
268	Me	$>C=NOCMe_2COOH$
269	Pn	$>C=NOCH_2COOH$
270	2-HOEt	$>CH_2$
271	2-HOEt	$>C=NOCMe_2COOH$
272	5-AcOPn	>C=NOH
273	2-HOEt	$>C=NOCH_2COOH$

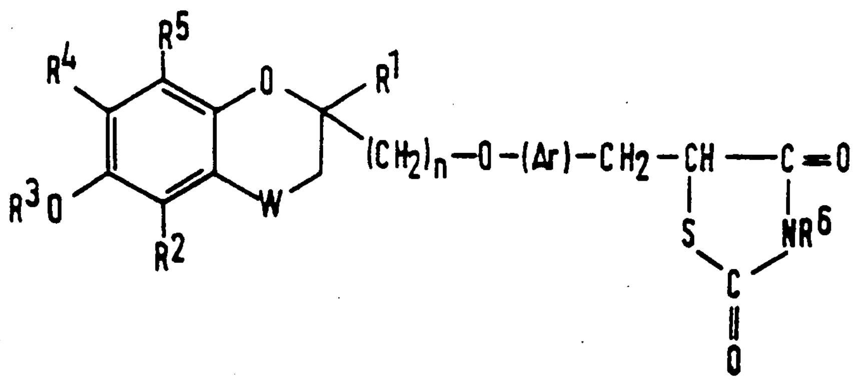
Compounds of formulae (I-14), (I-15), (I-16) and (I-17):



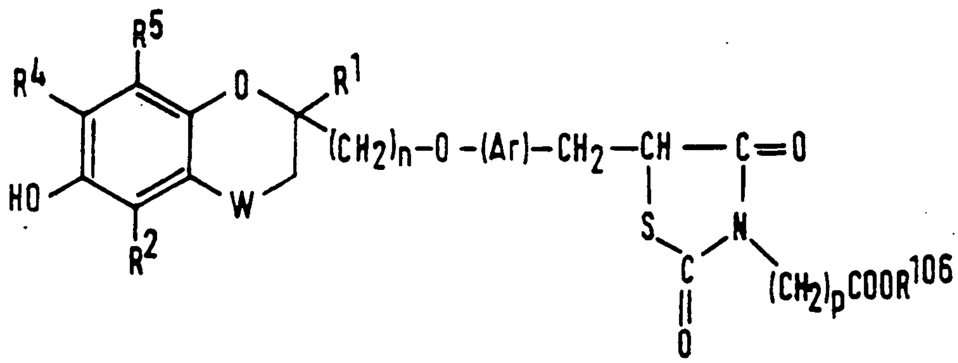
(I-14)



(I-15)



(I-16)



(I-17)

are as defined in Tables 14, 15, 16 and 17, respectively:

Table 14

Cpd. No.	R^1	R^2	R^4	R^5	R^{103}	W	Ar	n	r
274	Me	Me	Me	Me	H	$>CH_2$	p-Phn	1	1
275	Me	Me	Me	Me	Me	$>CH_2$	p-Phn	1	1
276	Me	Me	Me	Me	Et	$>CH_2$	p-Phn	1	1
277	Me	Me	Me	Me	tBu	$>CH_2$	p-Phn	1	1
278	Me	Me	Me	Me	H	>C=O	p-Phn	1	1
279	Me	Me	Me	Me	Me	>C=O	p-Phn	1	1
280	Me	Me	Me	Me	Et	>C=O	p-Phn	1	1
281	Me	Me	Me	Me	iPr	>C=O	p-Phn	1	1
282	Me	Me	Me	Me	tBu	>C=O	p-Phn	1	1
283	Me	Me	Me	Me	H	>CH-OH	p-Phn	1	1
284	Me	Me	Me	Me	H	>C=NOH	p-Phn	1	1

Table 14 (cont)

Table 14 (cont)

Cpd. No.	R^1	R^2	R^4	R^5	R^{103}	W	Ar	n	r
285	Me	Me	Me	Me	Et	>C=NOH	p-Phn	1	1
286	Me	Me	Me	Me	tBu	>C=NOH	p-Phn	1	1
287	Me	Me	Me	Me	H	>C=NOCH$_2$COOH	p-Phn	1	1
288	Me	Me	Me	Me	Et	>C=NOCH$_2$COOEt	p-Phn	1	1
289	Me	Me	Me	Me	tBu	>C=NOCH$_2$COOtBu	p-Phn	1	1
290	Me	Me	Me	Me	H	>C=NOCMe$_2$COOH	p-Phn	1	1
291	Me	Me	Me	Me	H	>C=NOH	p-Phn	2	1
292	Me	Me	Me	Me	H	>CH$_2$	p-Phn	1	2
293	Me	Me	Me	Me	H	>CH$_2$	m-Phn	1	1
294	Me	Me	Me	Me	H	>CH$_2$	2,5-Pydi	1	1
295	Me	Me	Me	Me	H	>C=O	2,5-Pydi	1	2
296	Me	Me	Me	Me	H	>C=NOCH$_2$COOH	p-Phn	2	2
297	Me	Me	Me	Me	H	>C=NOH	2,5-Pydi	1	1

Table 14 (cont)

Cpd. No.	R^1	R^2	R^4	R^5	R^{103}	W	Ar	n	r
298	Me	Me	Me	Me	H	>CH·OH	2,5-Pydi	3	3
299	Me	Me	Me	Me	H	$>C=NO(CH_2)_2COOH$	p-Phn	1	1
300	Me	Me	Me	Me	H	$>C=NO(CH_2)_3COOH$	p-Phn	1	1
301	Me	H	tBu	H	H	$>CH_2$	p-Phn	1	1
302	Me	H	tBu	H	Et	$>CH_2$	p-Phn	1	1
303	Me	H	tBu	H	t-Bu	$>CH_2$	p-Phn	1	1
304	Me	H	tBu	H	H	>C=O	p-Phn	1	1
305	Me	H	tBu	H	H	>C=NOH	p-Phn	1	1
306	Me	H	tBu	H	Et	>C=NOH	p-Phn	1	1
307	Me	H	tBu	H	H	$>C=NOCH_2COOH$	p-Phn	1	1
308	Me	H	tBu	H	H	$>C=NOCMe_2COOH$	p-Phn	1	1
309	Me	H	tBu	H	H	$>CH_2$	2,5-Pydi	1	1
310	Me	H	tBu	H	H	>C=NOH	2,5-Pydi	1	1
311	Me	H	tBu	H	H	$>C=NOCH_2COOH$	2,5-Pydi	1	1

Table 14 (cont)

Cpd. No.	R^1	R^2	R^4	R^5	R^{103}	W	Ar	n	r
312	Et	<u>i</u>Pr	<u>i</u>Pr	H	Me	>C=NO$(CH_2)_3$COOH	p-Phn	1	1
313	Pr	H	Me	H	H	>CH_2	p-Phn	1	1
314	<u>i</u>Pr	H	<u>t</u>Bu	H	H	>C=NOH	m-Phn	1	1
315	<u>i</u>Bu	Me	Me	Me	H	>CH_2	p-Phn	1	1
316	<u>i</u>Bu	Me	Me	Me	H	>C=NOH	p-Phn	1	1
317	Oc	Me	Me	Me	H	>CH_2	p-Phn	1	1
318	Oc	Me	Me	Me	H	>C=NOCH_2COOH	2,5-Pydi	2	1
319	Me	Me	MeO	MeO	H	>CH_2	p-Phn	1	1
320	Me	Me	MeO	MeO	H	>C=NOH	p-Phn	1	1
321	Me	H	TMB	H	H	>CH_2	p-Phn	1	1
322	Me	H	TMB	H	H	>C=O	p-Phn	1	1
323	Me	H	TMB	H	H	>C=NOH	p-Phn	1	1
324	Me	H	TMB	H	H	>C=NOCH_2COOH	p-Phn	1	1

Table 15

Cpd. No.	R^1	R^2	R^4	R^5	R^{103}	W	Ar	n	r
325	Bu	H	TMB	H	H	$>CH_2$	2,5-Pydi	1	3
326	5,5-DMH	Me	Me	Me	H	$>CH_2$	p-Phn	1	1
327	Me	Me	Me	Me	Et	$>CH_2$	p-Phn	1	5
328	Me	Me	Me	Me	H	>C=NOBz	p-Phn	1	1

Table 15 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	Ar	n
329	Me	H	$HO(CH_2)_2OCOCH_2$-	TMB	H	$>CH_2$	p-Phn	1
330	Pr	H	$HO(CH_2)_2OCOCH_2$-	$\underline{t}$Bu	H	>C=O	p-Phn	1
331	Et	H	$HO(CH_2)_3OCOCH_2$-	Me	H	>C=NOH	p-Phn	1
332	Me	Me	$HO(CH_2)_5OCOCH_2$-	Me	Me	$>C=NOCH_2COOH$	p-Phn	1
333	Me	Me	$MeO(CH_2)_2OCOCH_2$-	Me	Me	$>CH_2$	p-Phn	1
334	Me	Me	$MeO(CH_2)_2OCOCH_2$-	Me	Me	>C=O	p-Phn	1
335	Me	Me	$MeO(CH_2)_2OCOCH_2$-	Me	Me	>C=NOH	p Phn	1
336	Me	Me	$MeO(CH_2)_2OCOCH_2$-	Me	Me	$>C=NOCH_2COOH$	p-Phn	1
337	Me	H	$MeO(CH_2)_2OCOCH_2$-	$\underline{t}$Bu	H	$>CH_2$	p-Phn	1
338	Me	H	$MeO(CH_2)_2OCOCH_2$-	$\underline{t}$Bu	H	>C=O	p-Phn	1

Table 15 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	Ar	n
339	Me	H	$MeO(CH_2)_2OCOCH_2$-	TMB	H	$>CH_2$	p-Phn	1
340	Me	H	$MeO(CH_2)_2OCOCH_2$-	TMB	H	>C=O	p-Phn	1
341	Me	Me	$MeO(CH_2)_2OCOCH_2$-	Me	Me	>CH·OH	p-Phn	1
342	Me	Me	$MeO(CH_2)_2OCOCH_2$-	Me	Me	>C=NOH	6-Me-1,3-Phn	1
343	3,3-DMB	Me	$EtO(CH_2)_2OCOCH_2$-	Me	Me	>CHOAc	p-Phn	1
344	Me	H	<u>i</u>$PrO(CH_2)_3OCOCH_2$	Me	H	$>C=NOCH_2COOEt$	p-Phn	1
345	5,5-DMH	H	$MeO\cdot(CH_2)_5OCOCH_2$	<u>i</u>Pr	H	$>C=NOCH_2COOH$	p-Phn	1
346	Me	Me	$AcO\text{-}(CH_2)_2O\text{-}CO\text{-}CH_2$-	Me	Me	$>CH_2$	2,5-Pydi	2
347	Bz	Me	$BozO(CH_2)_2OCOCH_2$-	Me	Me	>C=O	p-Phn	1
348	Me	Me	$MeO(CH_2)_2OCO(CH_2)_2$-	MeO	MeO	$>CH_2$	p-Phn	1
349	7,7-DMO	Me	$MeO(CH_2)_2OCO(CH_2)_3$-	Me	Me	>C=O	6-Me-1,3-Phn	1
350	Me	Me	$MeO(CH_2)_2OCO(CH_2)_5$-	Me	Me	$>CH_2$	p-Phn	3
351	Me	Me	MeOOC-CH(Me)-	Me	Me	$>CH_2$	p-Phn	1

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	Ar	n
352	Me	Me	$MeOOC-CH(Me)CH_2-$	Me	Me	>C=NOH	p-Phn	1
353	Me	Me	$MeOOC-CMe_2-$	Me	Me	$>CH_2$	p-Phn	1
354	Me	Me	$EtOOC-CMe_2-$	Me	Me	$>CH_2$	p-Phn	1
355	Me	Me	$EtOOC-CMe_2-$	Me	Me	>C=O	p-Phn	1
356	Me	Me	$EtOOC-CMe_2-$	Me	Me	>C=NOH	p-Phn	1
357	Me	Me	$EtOOC-CMe_2-$	Me	Me	$>C=NOCH_2COOH$	p-Phn	1
358	Me	Me	$EtOOC-CMe_2-$	Me	Me	$>C=NOCH_2COOEt$	p-Phn	1
359	Me	H	$EtOOC-CMe_2-$	tBu	H	$>CH_2$	p-Phn	1
360	Me	H	$EtOOC-CMe_2-$	tBu	H	>C=O	p-Phn	1
361	Me	H	$EtOOC-CMe_2-$	tBu	H	>C=NOH	p-Phn	1

Table 15 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	Ar	n
362	Me	H	EtOOC-CMe_2-	<u>t</u>Bu	H	>C=$NOCH_2COOH$	p-Phn	1
363	Me	H	EtOOC-CMe_2-	<u>t</u>Bu	H	>C=$NOCH_2COOEt$	p-Phn	1
364	Me	Me	EtOOC-CMe_2-	Me	Me	>C=$NOCMe_2COOEt$	p-Phn	1
365	Me	Me	HOOC-CMe_2-	Me	Me	>CH_2	p-Phn	1
366	Me	Me	HOOC-CMe_2-	Me	Me	>C=O	p-Phn	1
367	Me	Me	HOOC-CMe_2-	Me	Me	>C=NOH	p-Phn	1
368	Me	Me	HOOC-CMe_2-	Me	Me	>C=$NOCH_2COOH$	p-Phn	1
369	Me	Me	HOOC-CMe_2-	Me	Me	>C=$NO(CH_2)_2COOH$	p-Phn	1
370	Me	Me	HOOC-CMe_2-	Me	Me	>C=$NOCMe_2COOH$	p-Phn	1
371	Me	H	HOOC-CMe_2-	<u>t</u>Bu	H	>CH_2	p-Phn	1
372	Me	H	HOOC-CMe_2-	<u>t</u>Bu	H	>C=O	p-Phn	1
373	Me	H	HOOC-CMe_2-	<u>t</u>Bu	H	>C=NOH	p-Phn	1
374	Me	H	HOOC-CMe_2-	TMB	H	>CH_2	p-Phn	1

Table 15 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	Ar	n
375	Me	H	HOOC·CMe_2-	TMB	H	>C=$NOCH_2COOH$	p-Phn	1
376	Me	Me	H_2NCOCH_2-	Me	Me	>C=O	p-Phn	1
377	Me	Me	$MeNHCOCH_2$-	Me	Me	>C=NOH	p-Phn	1
378	Me	H	Me_2NCOCH_2-	tBu	H	>CH_2	p-Phn	1
379	Me	Me	Et(Me)$NCOCH_2$-	Me	Me	>C=NOBoz	p-Phn	1
380	Me	Me	Mor$COCH_2$-	Me	Me	>C=$NOCMe_2COOH$	p-Phn	1
381	Me	Me	1-Pip$COCH_2$-	Me	Me	>C=$NOCH_2COOH$	p-Phn	1
382	Me	Me	1-Pyl$COCH_2$-	Me	Me	>C=NOBz	6 Me-1,3-Phn	1
383	Me	H	1-Piz$COCH_2$-	TMB	H	>CH_2	p-Phn	1
384	Me	Me	4-Me-1-Piz$COCH_2$-	Me	Me	>CH_2	p-Phn	1
385	Me	Me	$Me_2NCOCH_2CH_2$-	Me	Me	>CH_2	p-Phn	2
386	Me	Me	Me_2NCO-CMe_2-	Me	Me	>C=O	p-Phn	1
387	Me	Me	$Me_2NCO(CH_2)_5$-	Me	Me	>C=NOH	p-Phn	1

Table 16

Cpd. No.	R^1	R^2	R^3	R^4	R^5	R^6	W	Ar	n
388	Me	Me	$HOOC-CH_2-$	Me	Me	Oc	$>C=NOH$	p-Phn	1
389	M	H	$EtOOC-CH_2-$	Me	H	5,5-DMH	$>C=O$	p-Phn	3
390	Me	Me	$MeOCH_2CH_2OCOCH_2-$	Me	Me	Me	$>C=NOCH_2COOH$	p-Phn	1
391	Me	Me	$AcOCH_2CH_2OCOCH_2-$	MeO	MeO	2-MeOEt	$>C=NOH$	2,5-Pydi	2
392	Me	Me	$HOOC-CMe_2$	Me	Me	Bu	$>CH_2$	5-Me-1,3-Phn	1
393	Me	H	$HOOC-CH_2CH_2-$	TMB	H	3,3-DMB	$>C=NOCMe_2COOH$	p-Phn	1
394	Me	Me	H_2NCOCH_2-	Me	Me	Dc	$>CH_2$	p-Phn	1
395	7,7-DMO	H	$Et(Me)NCOCH_2$	<u>t</u>Bu	H	<u>i</u>Bu	$>C=NOCH_2COOEt$	p-Phn	1
396	Me	Me	H	Me	Me	Et	$>CH_2$	p-Phn	1
397	3,3-DMB	H	Me	TMB	H	Pr	$>C=NOCMe_2COOH$	p-Phn	1
398	Me	Me	Ac	Me	Me	<u>i</u>Pr	$>C=NOH$	p-Phn	1
399	Me	H	Me	<u>t</u>Bu	H	Bu	$>C=NOCH_2COOH$	p-Phn	1
400	Me	Me	H	Me	Me	2-OHEt	$>CH_2$	p-Phn	1

Table 17

Cpd No.	R^1	R^2	R^4	R^5	R^{106}	W	Ar	n	p
401	Me	Me	Me	Me	H	$>CH_2$	p-Phn	1	1
402	Me	Me	Me	Me	Me	$>CH_2$	p-Phn	1	1
403	Me	Me	Me	Me	Et	$>CH_2$	p-Phn	1	1
404	Me	Me	Me	Me	<u>t</u>Bu	$>CH_2$	p-Phn	1	1
405	Me	Me	Me	Me	H	>C=O	p-Phn	1	1
406	Me	Me	Me	Me	Me	>C=O	p-Phn	1	1
407	Me	Me	Me	Me	<u>i</u>Pr	>C=O	p-Phn	1	1
408	Me	Me	Me	Me	<u>t</u>Bu	>C=O	p-Phn	1	1
409	Me	Me	Me	Me	H	>CHOH	p-Phn	1	1
410	Me	Me	Me	Me	H	>C=NOH	p-Phn	1	1
411	Me	Me	Me	Me	<u>t</u>Bu	>C=NOH	p-Phn	1	1
412	Me	Me	Me	Me	H	$>C=NOCH_2COOH$	p-Phn	1	1
413	Me	Me	Me	Me	H	$>C=NOCH_2COOEt$	p-Phn	1	1
414	Me	Me	Me	Me	<u>t</u>Bu	$>C=NOCH_2COOt\text{-}Bu$	p-Phn	1	1
415	Me	Me	Me	Me	H	>C=NOH	p-Phn	2	1

Table 17 (cont)

Table 17 (cont)

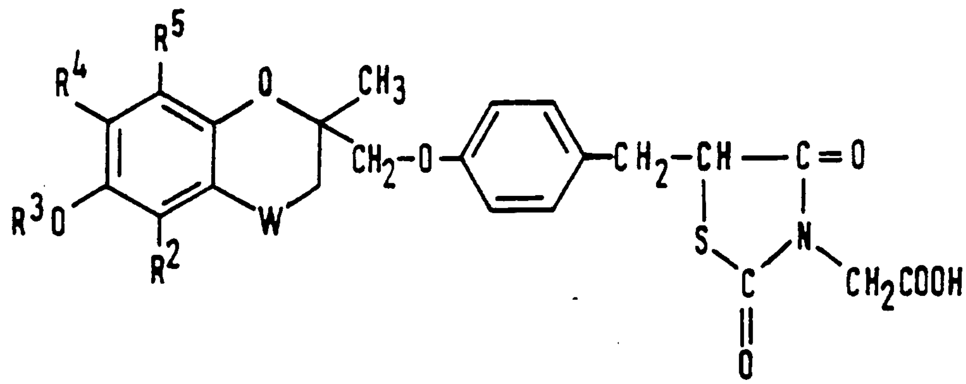
Cpd No.	R^1	R^2	R^4	R^5	R^{106}	W	Ar	n	p
416	Me	Me	Me	Me	H	$>CH_2$	p-Phn	1	2
417	Me	Me	Me	Me	H	$>CH_2$	m-Phn	1	1
418	Me	Me	Me	Me	H	$>CH_2$	2,5-Pydi	1	1
419	Me	Me	Me	Me	H	>C=O	2,5-Pydi	1	2
420	Me	Me	Me	Me	H	$>C=NOCH_2COOH$	p-Phn	2	2
421	Me	Me	Me	Me	H	>C=NOH	2,5-Pydi	1	1
422	Me	Me	Me	Me	H	>CHOH	2,5-Pydi	3	3
423	Me	Me	Me	Me	H	$>C=NO(CH_2)_2COOH$	p-Phn	1	1
424	Me	Me	Me	Me	H	$>C=NO(CH_2)_3COOH$	p-Phn	1	1
425	Me	H	<u>t</u>Bu	H	H	$>CH_2$	p-Phn	1	1
426	Me	H	<u>t</u>Bu	H	<u>t</u>Bu	$>CH_2$	p-Phn	1	1
427	Me	H	<u>t</u>Bu	H	H	>C=O	p-Phn	1	1
428	Me	H	<u>t</u>Bu	H	H	>C=NOH	p-Phn	1	1

Table 17 (cont)

Cpd No.	R^1	R^2	R^4	R^5	R^{106}	W	Ar	n	p
429	Me	H	tBu	H	H	$>C=NOCH_2COOH$	p-Phn	1	1
430	Me	H	tBu	H	H	$>CH_2$	2,5-Pydi	1	1
431	Me	H	tBu	H	H	$>C=NOH$	2,5-Pydi	1	1
432	Me	H	tBu	H	H	$>C=NOCH_2COOH$	2,5-Pydi	1	1
433	Et	iPr	iPr	H	Me	$>C=NO(CH_2)_3COOH$	p-Phn	1	1
434	Pr	H	Me	H	H	$>CH_2$	p-Phn	1	1
435	iPr	H	tBu	H	H	$>C=NOH$	m-Phn	1	1
436	iBu	Me	Me	Me	H	$>CH_2$	p-Phn	1	1
437	iBu	Me	Me	Me	H	$>C=NOH$	p-Phn	1	1
438	Oc	Me	Me	Me	H	$>CH_2$	p-Phn	1	1
439	Oc	Me	Me	Me	H	$>C=NOCH_2COOH$	2,5-Pydi	2	1
440	Me	Me	MeO	MeO	H	$>CH_2$	p-Phn	1	1
441	Me	Me	MeO	MeO	H	$>C=NOH$	p-Phn	1	1
442	Me	H	TMB	H	H	$>CH_2$	p-Phn	1	1

Cpd No.	R^1	R^2	R^4	R^5	R^{106}	W	Ar	n	p
443	Me	H	TMB	H	H	>C=O	p-Phn	1	1
444	Me	H	TMB	H	H	>C=NOH	p-Phn	1	1
445	Me	H	TMB	H	H	$>C=NOCH_2COOH$	p-Phn	1	1
446	Bu	H	TMB	H	H	$>CH_2$	2,5-Pydi	1	3

Compounds of formula (I-18):



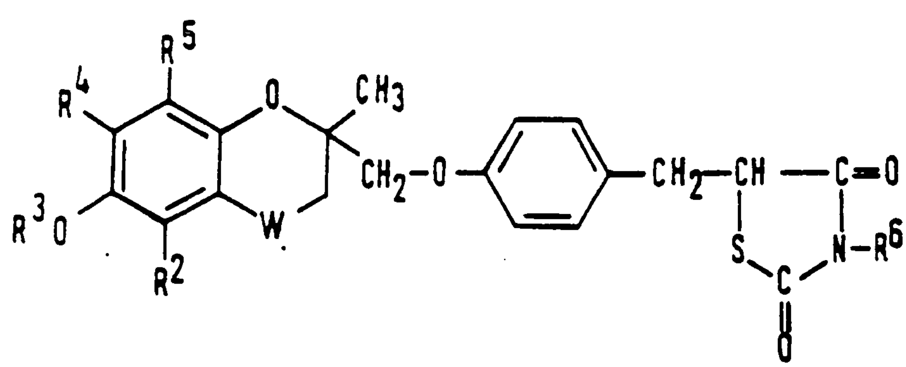
(I-18)

are as defined in Table 18:

Table 18

Cpd No.	R^2	R^3	R^4	R^5	W
447	Me	Me	Me	Me	>C=NOCH$_2$COOH
448	Me	Ac	Me	Me	>C=NOCH$_2$COOH
449	Me	MeOCH$_2$-	Me	Me	>CH$_2$
450	H	Boz	<u>t</u>Bu	H	>C=NOH
451	Me	EtOOCCH$_2$-	Me	Me	>C=N-O(4-MeBz)

Compounds of formula (I-19):



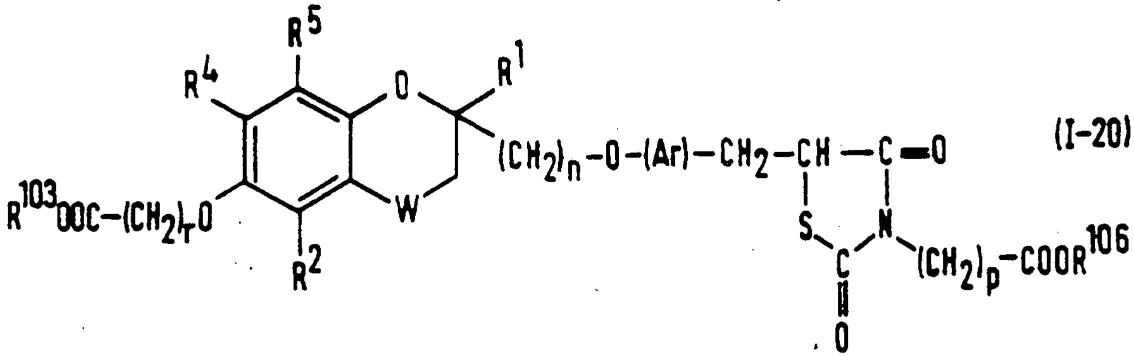
(I-19)

are as defined in Table 19:

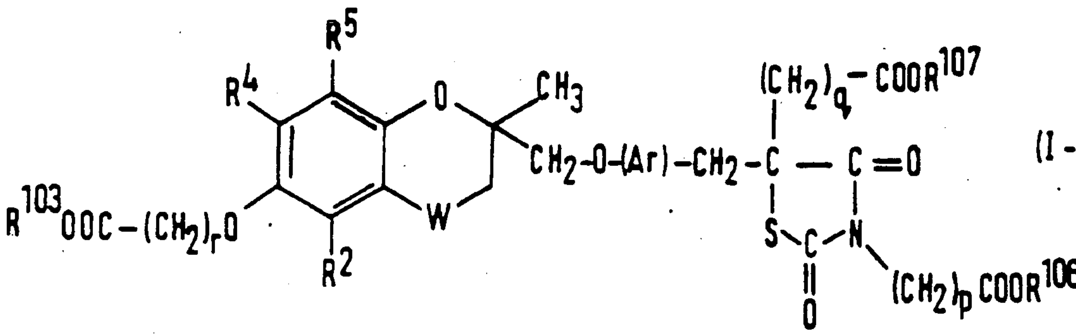
Table 19

Cpd No.	R^2	R^3	R^4	R^5	R^6	W
452	Me	Ac	Me	Me	$-CH_2COOH$	$>CH_2$
453	Me	Ac	Me	Me	$-CH_2COOMe$	$>CH_2$
454	Me	Ac	Me	Me	$-CH_2COOt\text{-}Bu$	$>CH_2$
455	Me	H	Me	Me	$-CMe_2COOH$	$>C{=}NOCMe_2COOH$
456	H	Ac	<u>t</u>Bu	H	$-CMe_2COOH$	$>C{=}NOCH_2COOH$
457	Me	H	Me	Me	$-CMe_2COOEt$	$>CH_2$
458	Me	H	Me	Me	$-CH_2CONMe_2$	$>CH_2$
459	Me	H	Me	Me	$-CH_2CO(4\text{-Me-1-Piz})$	$>CH_2$
460	Me	$HOOCCMe_2$-	Me	Me	$-CH_2COOH$	$>C{=}NOBz$

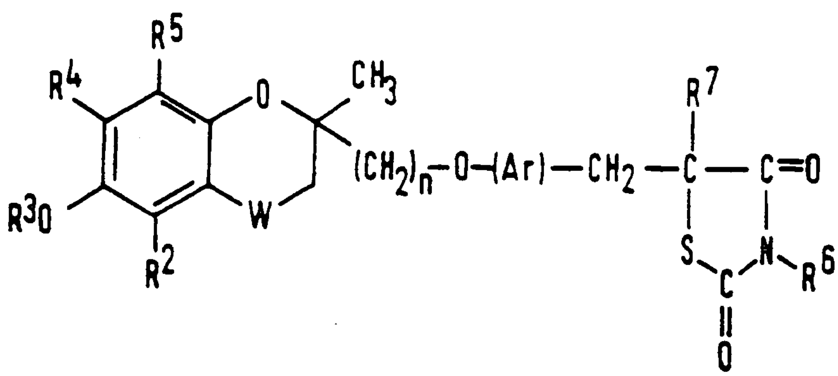
Compounds of formulae (I-20), (I-21), (I-22), (I-23) and (I-24):



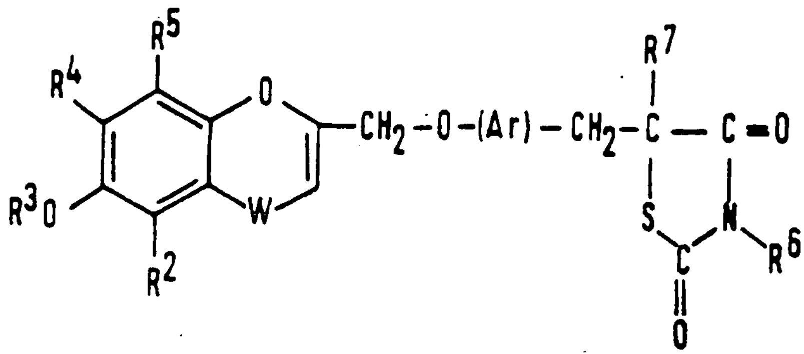
(I-20)



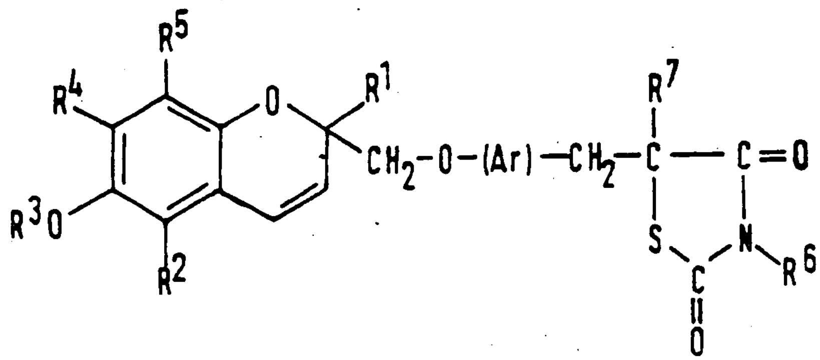
(I-21)



(I-22)



(I-23)



(I-24)

are as defined in Tables 20, 21, 22, 23 and 24, respectively:

Table 20

Table 20 (cont)

Cpd No.	R^1	R^2	R^4	R^5	R^{103}	R^{106}	W	Ar	n	r	p
461	Me	Me	Me	Me	H	H	$>CH_2$	p-Phn	1	1	1
462	Me	Me	Me	Me	Et	Et	$>CH_2$	p-Phn	1	1	1
463	Me	Me	Me	Me	$\underline{t}$Bu	$\underline{t}$Bu	$>CH_2$	p-Phn	1	1	1
464	Me	Me	Me	Me	H	H	>C=O	p-Phn	1	1	1
465	Me	Me	Me	Me	Me	Me	>C=O	p-Phn	1	1	1
466	Me	Me	Me	Me	$\underline{t}$Bu	$\underline{t}$Bu	>C=O	p-Phn	1	1	1
467	Me	Me	Me	Me	H	H	>C=NOH	p-Phn	1	1	1
468	Me	Me	Me	Me	$\underline{t}$Bu	$\underline{t}$Bu	>C=NOH	p-Phn	1	1	1
469	Me	Me	Me	Me	H	H	$>C=NOCH_2COOH$	p-Phn	1	1	1
470	Me	Me	Me	Me	H	H	$>C=NOCH_2COOEt$	p-Phn	1	1	1
471	Me	Me	Me	Me	$\underline{t}$Bu	$\underline{t}$Bu	$>C=NOCH_2COOt\text{-}Bu$	p-Phn	1	1	1
472	Me	Me	Me	Me	H	H	$>CH_2$	p-Phn	1	2	2
473	Me	Me	Me	Me	H	H	$>CH_2$	p-Phn	2	1	1
474	Me	Me	Me	Me	H	H	>C=O	p-Phn	1	2	1
475	Me	Me	Me	Me	H	H	>C=NOH	p-Phn	2	1	2

Table 20 (cont)

Cpd. No.	R^1	R^2	R^4	R^5	R^{103}	R^{106}	W	Ar	n	r	p
476	Me	Me	Me	Me	H	H	$>CH_2$	m Phn	1	3	3
477	Me	Me	Me	Me	H	H	$>CH_2$	2,5-Pydi	1	1	1
478	Me	Me	Me	Me	H	H	$>C=O$	2,5-Pydi	1	1	1
479	Me	Me	Me	Me	H	H	$>C=NOH$	2,5-Pydi	1	1	1
480	Me	Me	Me	Me	H	H	$>C=NOCH_2COOH$	2,5-Pydi	1	1	1
481	Me	Me	Me	Me	Et	<u>i</u>Pr	$>C=NOCH_2COOtBu$	2,5-Pydi	1	1	1
482	Me	Me	Me	Me	H	H	$>CH_2$	2,5 Pydi	3	2	2
483	Me	Me	Me	Me	H	H	$>C=NO(CH_2)_2COOH$	2,5 Pydi	1	2	2
484	Me	H	<u>t</u>Bu	H	H	H	$>CH_2$	p-Phn	1	1	1
485	Me	H	<u>t</u>Bu	H	Et	Et	$>CH_2$	p-Phn	1	1	1
486	Me	H	<u>t</u>Bu	H	<u>t</u>Bu	<u>t</u>Bu	$>CH_2$	p-Phn	1	1	1
487	Me	H	<u>t</u>Bu	H	H	H	$>C=O$	p-Phn	1	1	1
488	Me	H	<u>t</u>Bu	H	<u>t</u>Bu	<u>t</u>Bu	$>C=O$	p-Phn	1	1	1

Table 20 (cont)

Cpd No.	R^1	R^2	R^4	R^5	R^{103}	R^{106}	W	Ar	n	r	p
489	Me	H	tBu	H	H	H	$>C=NOH$	p-Phn	1	1	1
490	Me	H	tBu	H	H	H	$>C=NOCH_2COOH$	p-Phn	1	1	1
491	Me	H	tBu	H	tBu	tBu	$>C=NOCH_2COOt\cdot Bu$	p-Phn	1	1	1
492	Me	H	tBu	H	H	H	$>C=NOCH_2COOH$	2,5-Pydi	1	1	1
493	Et	Me	Me	Me	H	H	$>C=NO(CH_2)_2COOH$	p-Phn	1	2	2
494	Pr	Me	Me	Me	H	H	$>C=O$	m-Phn	2	1	1
495	iPr	H	Me	H	H	H	$>CH_2$	p-Phn	2	3	3
496	iBu	Me	Me	Me	H	H	$>C=NOCH_2COOH$	2,5 Pydi	1	1	1
497	Oc	Me	Me	Me	H	H	$>C=O$	p-Phn	1	1	1
498	Me	Me	MeO	MeO	H	H	$>CH_2$	p-Phn	1	1	1
499	Me	Me	MeO	MeO	H	H	$>C=O$	p-Phn	1	1	1
500	Me	H	TMB	H	H	H	$>CH_2$	p-Phn	1	1	1
501	Me	H	TMB	H	H	H	$>C=O$	p-Phn	1	1	1

Table 21

Cpd No.	R^1	R^2	R^4	R^5	R^{103}	R^{106}	W	Ar	n	r	p
502	Me	H	TMB	H	H	H	>C=NOH	p-Phn	1	1	1
503	Me	H	TMB	H	H	H	$>C=NOCH_2COOH$	p-Phn	1	1	1
504	Me	H	TMB	H	H	H	$>C=NOCH_2COOH$	2,5-Pydi	1	1	1

Table 21 (cont)

Cpd No.	R^2	R^4	R^5	R^{103}	R^{106}	R^{107}	W	Ar	r	p	q
505	Me	Me	Me	H	H	H	$>CH_2$	p Phn	1	1	1
506	Me	Me	Me	Et	Et	Et	$>CH_2$	p Phn	1	1	1
507	Me	Me	Me	<u>t</u>Bu	<u>t</u>Bu	<u>t</u>Bu	$>CH_2$	p-Phn	1	1	1
508	Me	Me	Me	H	H	H	>C=O	p-Phn	1	1	1
509	Me	Me	Me	<u>t</u>Bu	<u>t</u>Bu	<u>t</u>Bu	>C=O	p-Phn	1	1	1
510	Me	Me	Me	H	H	H	>C=NOH	p-Phn	1	1	1
511	Me	Me	Me	<u>t</u>Bu	<u>t</u>Bu	<u>t</u>Bu	>C=NOH	p Phn	1	1	1
512	Me	Me	Me	H	H	H	$>C=NOCH_2COOH$	p-Phn	1	1	1
513	Me	Me	Me	Et	Et	Et	$>C=NOCH_2COOEt$	p-Phn	1	1	1
514	Me	Me	Me	H	H	H	$>CH_2$	p-Phn	2	3	4

Table 22

Cpd No.	R^2	R^4	R^5	R^{103}	R^{106}	R^{107}	W	Ar	r	p	q
515	Me	Me	Me	H	H	H	>C=NOH	2,5-Pydi	1	1	1
516	Me	Me	Me	H	H	H	>C=NOCH$_2$COOH	2,5-Pydi	1	1	1
517	Me	Me	Me	Et	Et	Et	>C=NOCH$_2$COOEt	2,5-Pydi	1	1	1
518	H	t-Bu	H	H	H	H	>CH$_2$	p-Phn	1	1	1
519	H	t-Bu	H	H	H	H	>C=O	p-Phn	1	1	1
520	H	t-Bu	H	H	H	H	>C=NOH	p-Phn	1	1	1
521	H	t-Bu	H	H	H	H	>C=NOCH$_2$COOH	2,5-Pydi	1	1	1
522	H	TMB	H	H	H	H	>C=NOH	p-Phn	1	1	1
523	H	TMB	H	H	H	H	>C=NOCH$_2$COOH	p-Phn	1	1	1

Cpd No.	R²	R³	R⁴	R⁵	R⁶	R⁷	W	Ar	n
524	Me	HOOCCMe$_2$-	Me	Me	-CMe$_2$COOH	CMe$_2$COOH	>C=NOCMe$_2$COOH	p-Phn	1
525	Me	HOOCCMe$_2$-	Me	Me	CMe$_2$COOH	CMe$_2$COOH	>C=NOCMe$_2$COOH	2,5-Pydi	1
526	Me	HOOCCMe$_2$-	Me	Me	-CMe$_2$COOH	-CMe$_2$COOH	>C=NOH	p-Phn	1
527	Me	HOOCCMe$_2$-	Me	Me	-CMe$_2$COOH	-CMe$_2$COOH	>CH$_2$	p-Phn	1
528	H	HOOCCMe$_2$-	_t_Bu	H	-CMe$_2$COOH	-CMe$_2$COOH	>CH$_2$	6-Me-1,3-Phn	2
529	Me	H$_2$NCOCH$_2$-	Me	Me	CH$_2$CONH$_2$	-CH$_2$CONH$_2$	>CH$_2$	p-Phn	1
530	Me	MorCOCH$_2$-	Me	Me	CH$_2$COMor	CH$_2$COMor	>C=NOCH$_2$COMor	p-Phn	1
531	Me	HOOCCH$_2$-	Me	Me	-CH$_2$CONH$_2$	CH$_2$CONH$_2$	>CH$_2$	p-Phn	1
532	Me	HOOCCMe$_2$-	Me	Me	-CH$_2$COMor	-CH$_2$COMor	>C=NOCH$_2$COMor	p-Phn	1

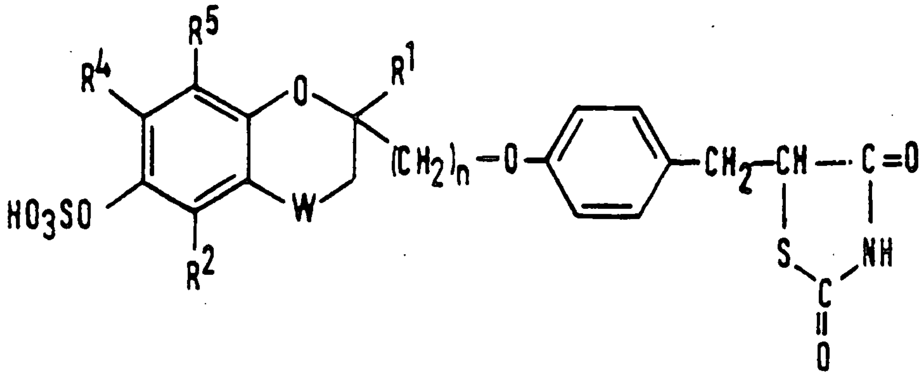
Table 23

Cpd No.	R^2	R^3	R^4	R^5	R^6	R^7	W_1	Ar
533	Me	$HOOCCH_2$-	Me	Me	H	H	>C=O	p-Phn
534	Me	$HOOCCH_2$-	Me	Me	$-CH_2COOH$	H	>C=N-OH	p-Phn
535	Me	$EtOOCCH_2$-	Me	Me	CH_2COOEt	$-CH_2COOEt$	$>C=NOCH_2COOEt$	p-Phn
536	Me	H	Me	Me	$-CH_2COOH$	H	$>C=NOCH_2COOH$	p-Phn
537	Me	$HOOCCMe_2$-	Me	Me	H	H	>C=O	p-Phn
538	H	$PipCOCH_2$-	t-Bu	H	$-CH_2COPip$	H	>C=O	2,5-Pydi

Table 24

Cpd No.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Ar
539	Me	Me	$MeOCH_2CH_2OOCCH_2$-	Me	Me	H	H	p-Phn
540	Me	Me	$HOOCCH_2$-	Me	Me	H	H	p-Phn
541	7,7-DMO	H	$HOOCCMe_2$-	tBu	H	-CMe_2COOH	-CMe_2COOH	2,5-Pydi
542	Me	Me	$MeOOCCH_2$-	Me	Me	H	H	p-Phn
543	Me	Me	2-HOEt	Me	Me	H	H	p-Phn
544	Bz	H	CH_3OCH_2-	TMB	H	-CMe_2COOEt	-CH_2COOt-Bu	6-Me-1,3-Phn
545	Me	Me	H	Me	Me	-CH_2COOH	-CH_2COOH	p-Phn

Compounds of formula (I-25):



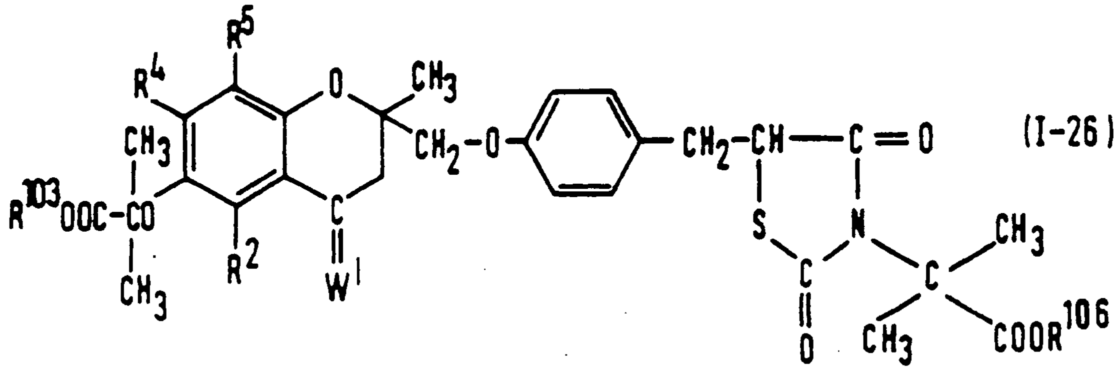
(I-25)

are as defined in Table 25:

Table 25

Cpd No.	R^1	R^2	R^4	R^5	n	W
546	Me	Me	Me	Me	1	>CH_2
547	Me	Me	Me	Me	1	>C=O
548	Me	H	tBu	H	1	>CH_2
549	Me	H	tBu	H	1	>C=O
550	Me	Me	Me	Me	2	>CH_2
551	Me	H	tBu	H	2	>CH_2
552	Et	Me	Me	Me	1	>CH_2
553	iBu	Me	Me	Me	1	>CH_2
554	iBu	Me	Me	Me	1	>C=O
555	Pn	Me	Me	Me	1	>CH_2
556	H	Me	Me	Me	1	>CH_2
557	Me	H	iPr	H	1	>CH_2
558	iBu	H	tBu	H	1	>CH_2
559	Oc	Me	Me	Me	1	>CH_2
560	Oc	Me	Me	Me	1	>C=O
561	Oc	H	tBu	H	1	>CH_2
562	Oc	H	tBu	H	1	>C=O
563	Me	H	TMB	H	1	>CH_2
564	Me	H	TMB	H	2	>CH_2
565	iBu	H	TMB	H	1	>CH_2
566	Oc	H	TMB	H	1	>CH_2

Compounds of formula (I-26):



(I-26)

are as defined in Table 26:

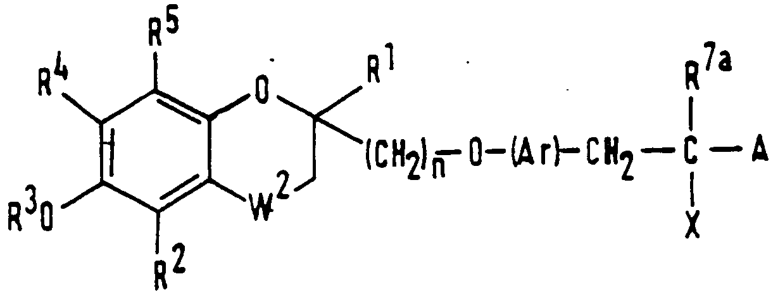
Table 26

Cpd. No.	R^2	R^{103}	R^4	R^5	R^{106}	W'
546	Me	H	Me	Me	H	$=NOCMe_2COOH$
547	H	H	<u>t</u>Bu	H	H	$=NOCH_2COOH$
548	Me	H	Me	Me	H	=NOH
549	Me	H	Me	Me	H	$=H_2$
550	Me	Et	Me	Me	Et	$=H_2$

Of the compounds listed above, preferred compounds are Compounds Nos. 5, 9, 10, 11, 12, 14, 15, 17, 23, 32, 39, 51, 52, 53, 56, 57, 118, 142, 159, 160, 174, 227, 274, 276, 278, 279, 280, 282, 284, 285, 287, 288, 301, 302, 305, 307, 401, 403, 405, 410, 412, 425, 428, 429, 461, 462, 464, 465, 467, 469, 484, 485, 487, 489, 490, 492, 505, 506, 508, 510, 512, 513, 518, 519, 520, 521, and 546. The more preferred compounds are Compounds Nos. 9, 10, 11, 12, 17, 23, 51, 52, 53, 56, 57, 118, 142, 159, 160, 174, 274, 284, 401, 405, 410, 461, 464, 467, 508 and 510, and the most preferred compounds are Compounds Nos. 9, 11, 142, 464, 467 and 510.

Also preferred are pharmaceutically acceptable salts of the above compounds.

The compounds of the invention (including those compounds defined above and covered by prior EP-A 0139421) may be prepared by reacting a compound of formula (II):



(II)

[in which:

R^1, R^2, R^3, R^4, R^5, n and Ar are as defined above;

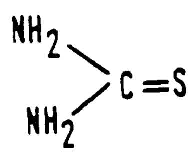
A represents a cyano group, a carboxy group, a C_2-C_6 alkoxycarbonyl group, a carbamoyl group or a group of formula -COOM where M represents a cation;

X represents a halogen atom;

R^{7a} represents a hydrogen atom or an unsubstituted C_1-C_{10} alkyl group; and

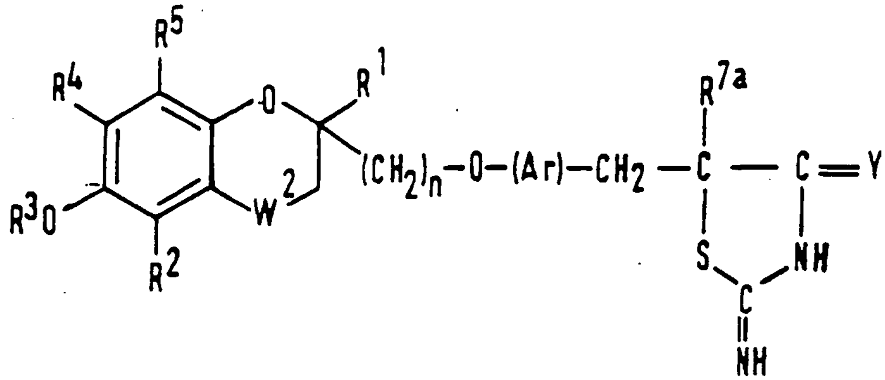
W^2 represents a methylene ($-CH_2-$) group or a carbonyl (>C=O) group]

with thiourea, which has the formula (III):



(III)

to give a compound of formula (V):



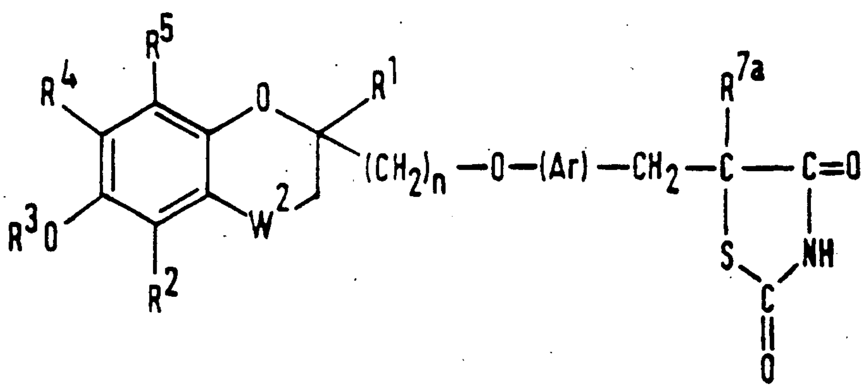
(V)

(in which:

R¹, R², R³, R⁴, R⁵, R⁷ᵃ, n, Ar and W² are as defined above; and

Y represents an oxygen atom or an imino group).

This compound may immediately be hydrolized under the prevailing reaction conditions; if it is not, then a separate hydrolysis step is required, to hydrolize the imino group at the 2-position of the thiazolidine ring and, where Y represents an imino group, to hydrolize that imino group also, to an oxygen atom, thereby giving the compound of formula (IV):



(IV)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n, Ar and W^2 are as defined above).

If necessary, subsequent steps may be carried out to replace various of the substituent groups by other groups within the definitions given above, employing the reactions described in more detail hereafter.

Where A represents a C_2-C_6 alkoxycarbonyl group (i.e. the alkoxy part has from 1 to 5 carbon atoms), examples of such groups include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and butoxycarbonyl groups. Where A represents a group of formula -COOM and M represents a cation, the nature of the cation is not critical to the invention, since it is eliminated in the course of the reaction. Preferably the cation is a metal ion, such as a sodium, potassium, calcium or aluminium ion, but it may also be an ammonium ion and other ions, including ions derived from organic bases, are possible, although not presently preferred.

X represents a halogen atom and, again, the nature of this is not critical, since the atom is eliminated in the course of the reaction. Most suitably, the halogen atom represented by X is a chlorine, bromine or iodine atom.

The reaction of the compound of formula (II) with the thiourea is preferably effected in the presence of a solvent. The nature of the solvent is not critical, provided that it has no adverse effect upon the reaction. Suitable solv nts include, for xample: alcohols, such as methanol, ethanol, propanol, butanol and ethylene glycol monomethyl ether;

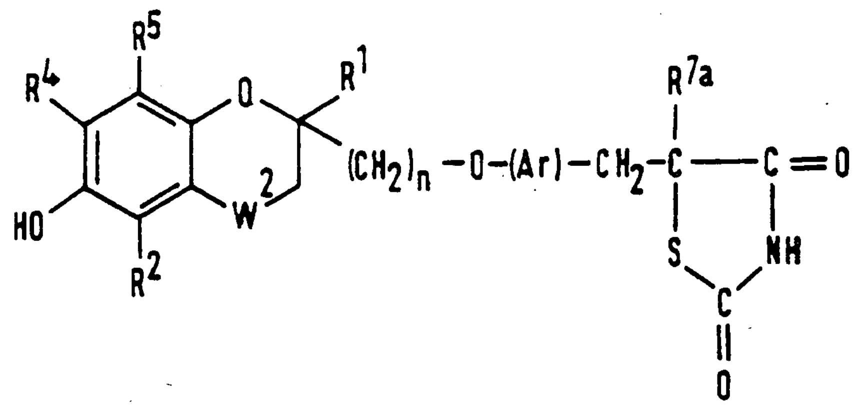
ethers, such as tetrahydrofuran or dioxane; ketones, such as acetone; dimethyl sulphoxide; sulphones, such as sulph lane; and amides, such as dimethylformamide.

Ther is no criticality as to the molar ratio of the compound of formula (II) to the thiourea and so conventional criteria apply to determine the most suitable proportions. Preferably the two reagents are employed in equimolar amounts or the thiourea is employed in excess, preferably a slight excess. The most suitable ratio of thiourea to compound of formula (II) is from 1:1 to 2:1.

The reaction temperature is not critical to the invention, although the optimum temperature will vary, depending upon the nature of the reagents and the solvent employed. In general, we prefer to carry out the reaction at the boiling point of the solvent or at a temperature within the range from 80 to 150°C. The time required for the reaction will vary, depending upon many factors, notably the reaction temperature and the nature of the reagents, but a period of from 1 to 20 hours will normally suffice.

Where hydrolysis of the resulting compound of formula (V) is required as a separate step, this may be effected by heating the compound of formula - (V) in a suitable solvent in the presence of water and of an acid. The nature of the solvent is not critical, provided that it has no adverse effect upon the reaction and examples of suitable solvents include: sulpholane; and alcohols, such as methanol, thanol or ethylene glycol monomethyl ether. Suitable acids include such organic acids as acetic acid and such mineral acids as sulphuric acid or hydrochloric acid. The amount of acid added is preferably from 0.1 to 10 moles, more preferably from 0.2 to 3 moles, per mole of the compound of formula (V). The water or aqueous solvent employed in this hydrolysis is preferably added in stoichiometric excess with respect to the compound of formula (V), preferably a large excess. The reaction temperature is not particularly critical, although we prefer to carry out the reaction at a temperature of from 50 to 100°C, at which temperature the reaction will normally be essentially complete within a period of from 2 to 20 hours.

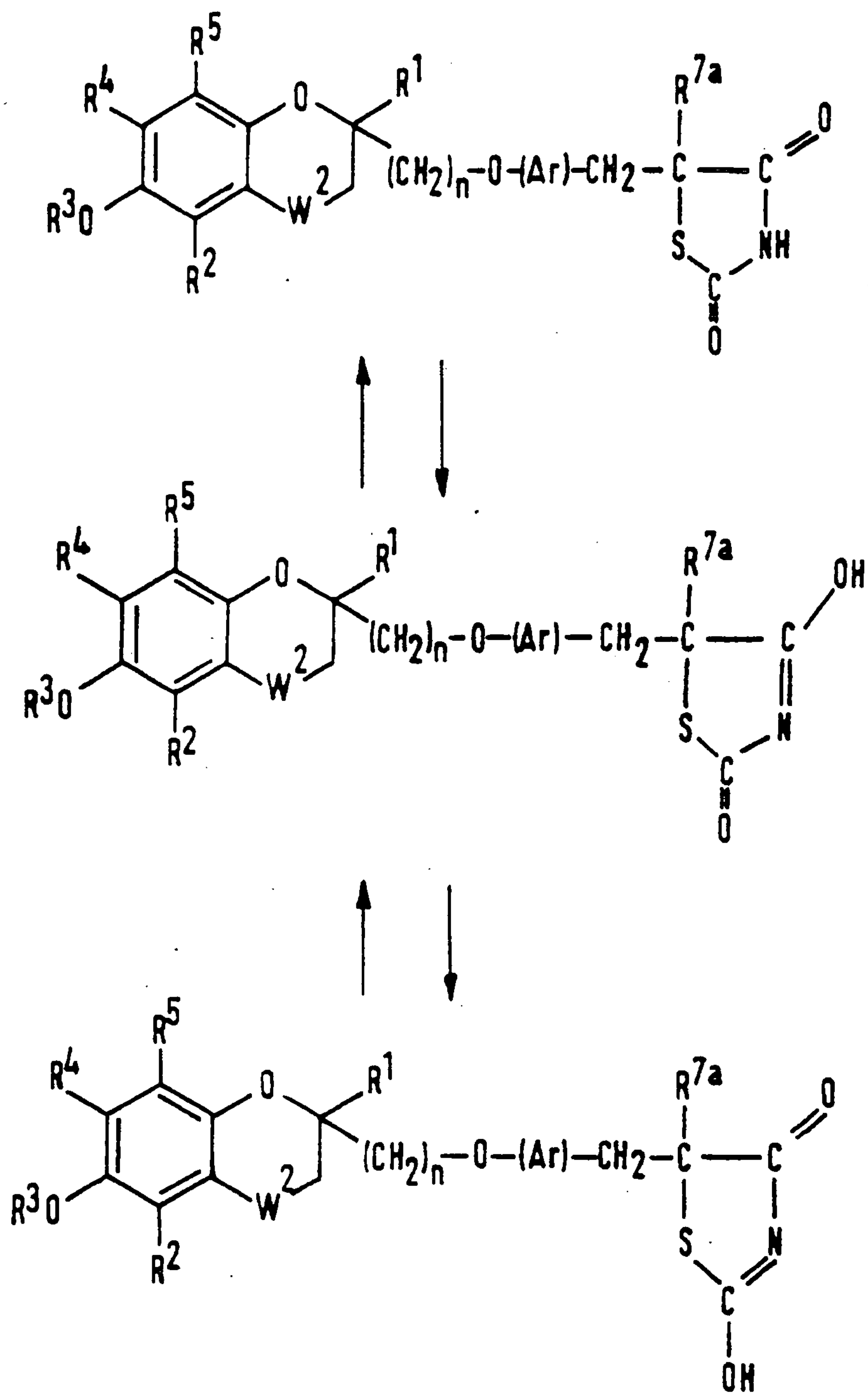
Where R^3 in the compound of formula (V) represents an acyl group, the hydrolysis step will often hydrolize this to a hydrogen atom, giving a compound of formula (IVH):



(IVH)

(in which R^1, R^2, R^4, R^5, R^{7a}, n, Ar and W^2 are as defined above); however, depending upon the precise reaction conditions and the nature of the acyl group represented by R^3, this hydrolysis may not take place or may take place to a limited extent only, so that the acyl group is kept intact. Similarly, other acyl groups within the compound of formula - (V) may or may not also be hydrolized.

Compounds of formula (IV) can exist in th following tautomeric forms:



although, for convenience, these are represented by a single formula (IV) herein. It will be appreciated that similar tautomeric forms xist in r lation to the imino compound of formula (V) and these likewise are shown herein by means of a singl formula only.

Those compounds of the invention which contain one or m r carboxy groups or which contain a phenolic hydroxy group [e.g. where R^3 represents a hydrogen atom, as in the compounds of formula -(IVH)] can form salts, in a conventional manner, with cations. There is no particular restriction on the nature of the cations employed to form such salts, except that, where the compounds of the invention are to be used for therapeutic purposes, the resulting salts should be pharmaceutically acceptable, which, as is well-known in the art, means that the resulting salts should not have a reduced activity (or unacceptably reduced activity) or an increased toxicity (or unacceptably increased toxicity) as compared with the parent compound. On the other hand, where the compounds are to be used for non-therapeutic purposes, e.g. where they are to be used as intermediates in the preparation of other compounds, even this restriction does not apply. Suitable salts include, for example: alkali metal salts, such as the sodium, potassium or lithium salts; alkaline earth metal salts, such as the calcium or magnesium salts; salts with other metals, especially trivalent metals, for example salts with aluminium, iron, cobalt, nickel or zinc; ammonium salts; salts with organic amines, for example the triethylamine or cyclohexylamine salts; and salts with basic amino acids, for example lysine or arginine. The compounds of the invention may be converted into such salts simply by a conventional reaction with an appropriate base.

Likewise, where the compounds of the invention contain a basic group, they can form acid addition salts. As with the salts mentioned above, where the compounds are to be used for therapeutic purposes, the salts should be pharmaceutically acceptable but, where they are to be used for non-therapeutic purposes, this restriction does not apply. Suitable acids for use in producing such salts include: inorganic acids, such as hydrochloric acid, sulphuric acid, nitric acid or phosphoric acid; organic carboxylic acids, such as acetic acid, tartaric acid, maleic acid, fumaric acid, malic acid, succinic acid, glutamic acid or aspartic acid; and organic sulphonic acids, such as p-toluenesulphonic acid or methanesulphonic acid. The compounds of the invention may be converted into such salts simply by a conventional reaction with an appropriate acid.

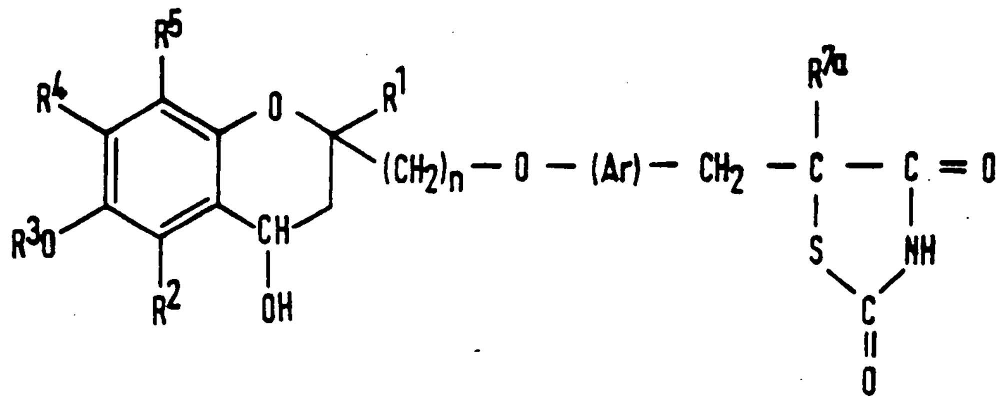
Furthermore, compounds of formula (IVH) can be converted into a corresponding ester by reaction with an acylating agent, normally an organic acid or reactive derivative thereof. Suitable reactive derivatives include the acid halides and acid anhydrides, especially the acid anhydrides. Where an acid itself is employed, we prefer to carry out the reaction in the presence, as catalyst, of a strong acid, for example a mineral acid (such as hydrochloric acid or sulphuric acid) or an organic sulphonic acid (such as p-toluenesulphonic acid).

Otherwise, the nature of the acylating agent employed depends upon the nature of the acyl group which it is desired to introduce, and these are defined above as the acyl groups which may be represented by R^3.

The reaction is preferably effected in the presence of an solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: ethers, such as diethyl ether, tetrahydrofuran or dioxane, aromatic hydrocarbons, such as benzene or toluene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptane; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; ketones, such as acetone or methyl ethyl ketone; amides, such as dimethylformamide or dimethylacetamide; organic bases, such as pyridine or triethylamine; sulphoxides, such as dimethyl sulphoxide; sulphones, such as sulpholane; water; and mixtures of any two or more thereof. There is no particular restriction on the ratio of the compound of formula (IVH) to the acylating agent, but we generally prefer to employ an excess, suitably a slight excess, of the acylating agent or an equimolar amount of the two reagents. In general, we would employ a molar ratio of acylating agent to compound of formula (IVH) of from 1:1 to 10:1.

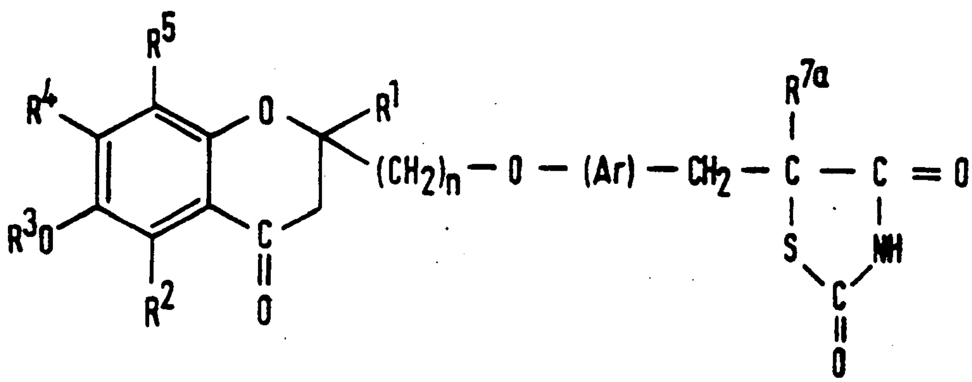
The reaction temperature is not critical and the reaction will take place over a wide range of temperatures; however, we generally prefer to carry out the reaction at a temperature of from 0°C to 100°C. The time required for the reaction will vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature, but, at a temperature within the recommended range, a period of from 5 minutes to 20 hours will normally suffice.

Compounds of the invention in which W represents a hydroxymethylene group, that is to say compounds of formula (VI):



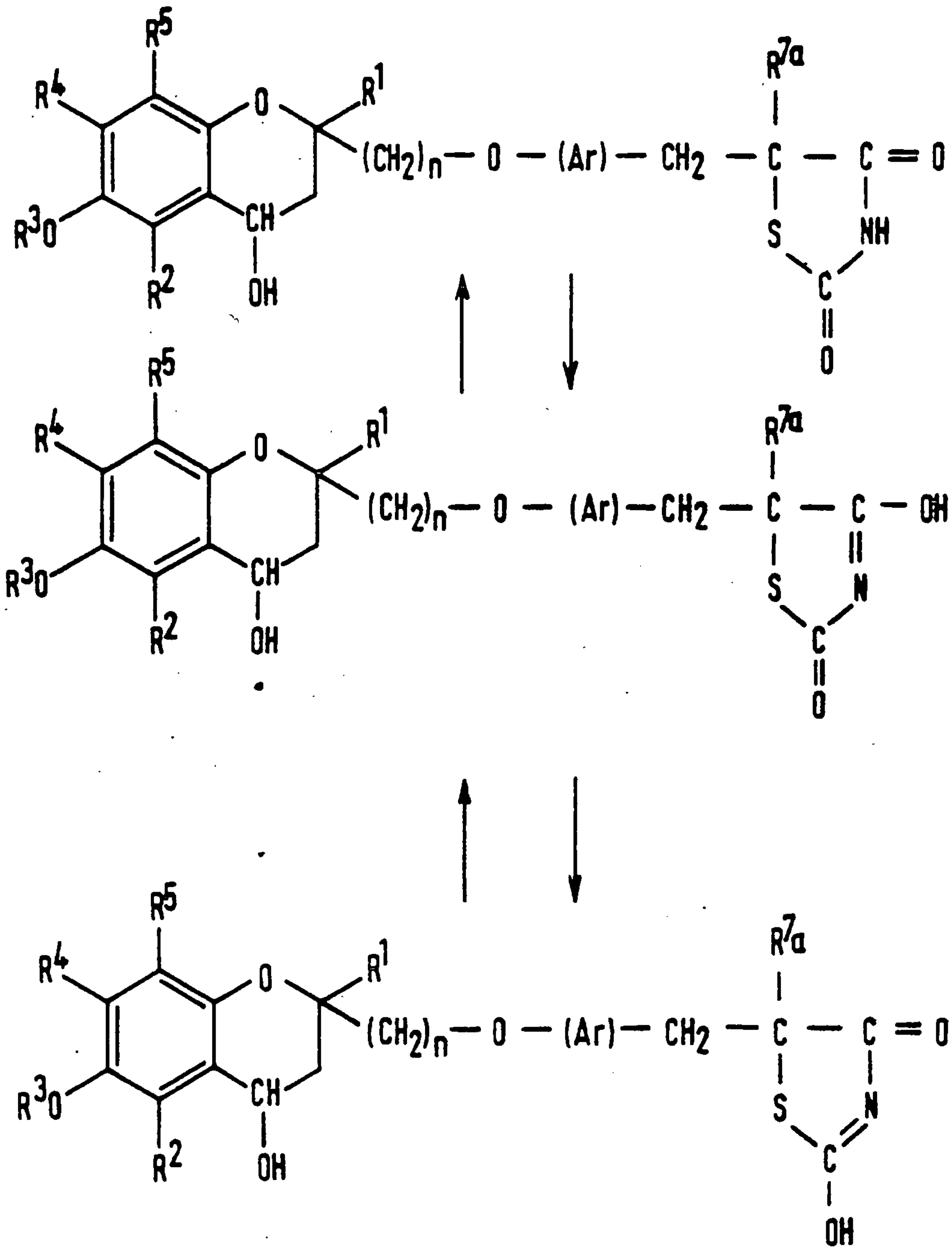
(VI)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n and Ar are as defined above), can be prepared by reacting a compound of formula (IV) or (IVH) in which W^2 represents a carbonyl group, that is to say a compound of formula (VII):



(VII)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n and Ar are as defined above) with a reducing agent, such as sodium borohydride or K-selectride, preferably sodium borohydride. The resulting compound of formula (VI) can exist in the following tautomeric forms:

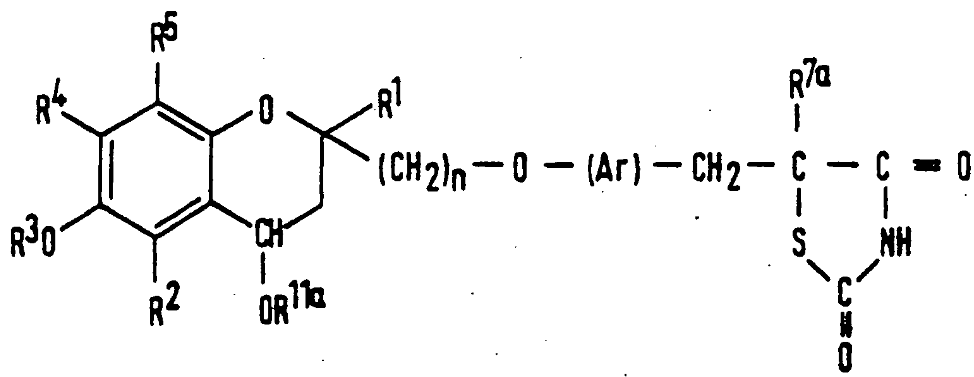


but, for convenience, these are all represented herein by the single formula (VI).

Reaction of the compound of formula (VII) with the reducing agent is preferably effected in the presence of a solvent. The nature of the solvent is not critical, provided that it has n adverse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether; and ethers, such as tetrahydrofuran or dioxane. There is also no criticality as to the ratio of the compound of formula (VII) to the reducing agent, although an excess of the reducing agent is generally preferred. In general, we prefer to employ a molar ratio of reducing ag nt to compound of formula (VII) of from 1:1 to 20:1.

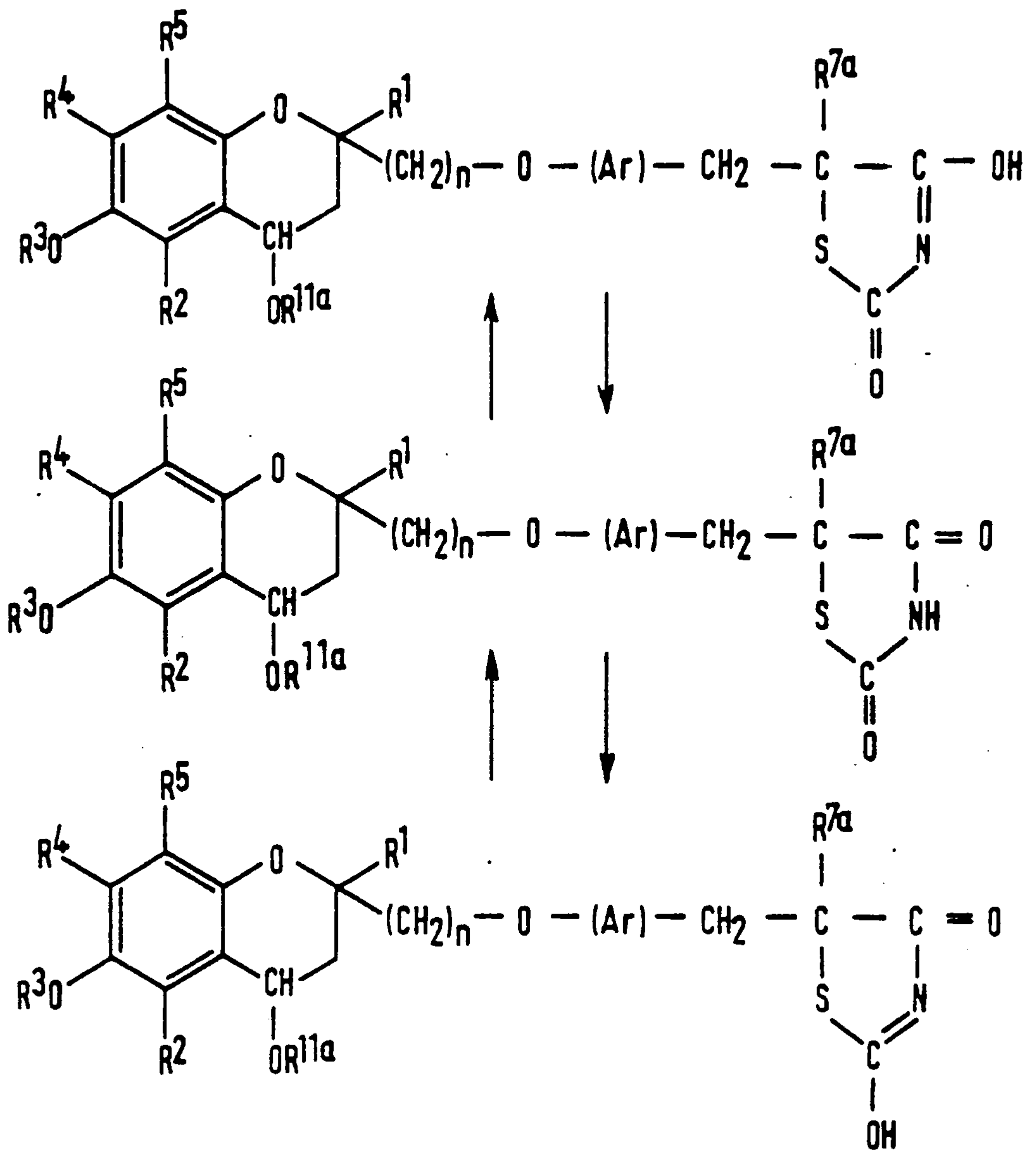
The reaction will take place over a wide range of temperatures and the particular reaction temperature chosen is not particularly critical. We generally prefer to carry out the reaction at a temperature of from 0°C to 100°C. The time required for the reaction will vary widely, depending upon many factors, notably the reaction temperature and the natur of the reducing agent, but a period of from 1 to 20 hours will normally suffice.

The resulting compounds of formula (VI) can, if desired, be converted to the corresponding acyl derivatives of formula (VIII):



(VIII)

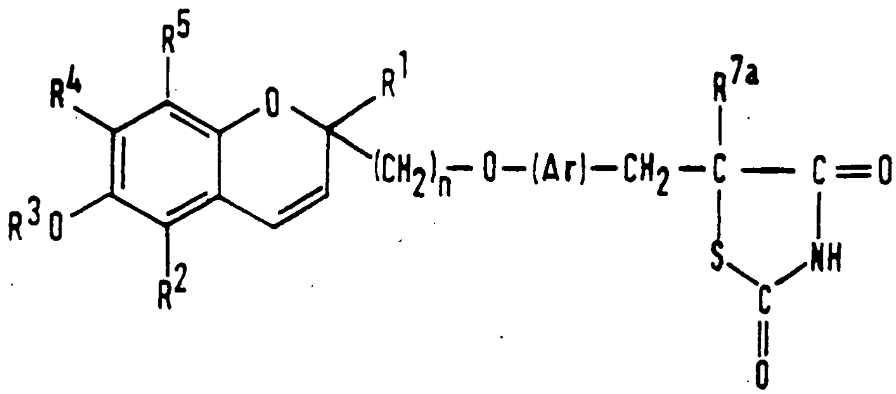
(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n and Ar are as defined above, and R^{11a} represents any one of the acyl groups included within the definition of R^{11}). These compounds can exist in the following tautomeric forms:



but, for convenience, they are all represented herein by a single formula only.

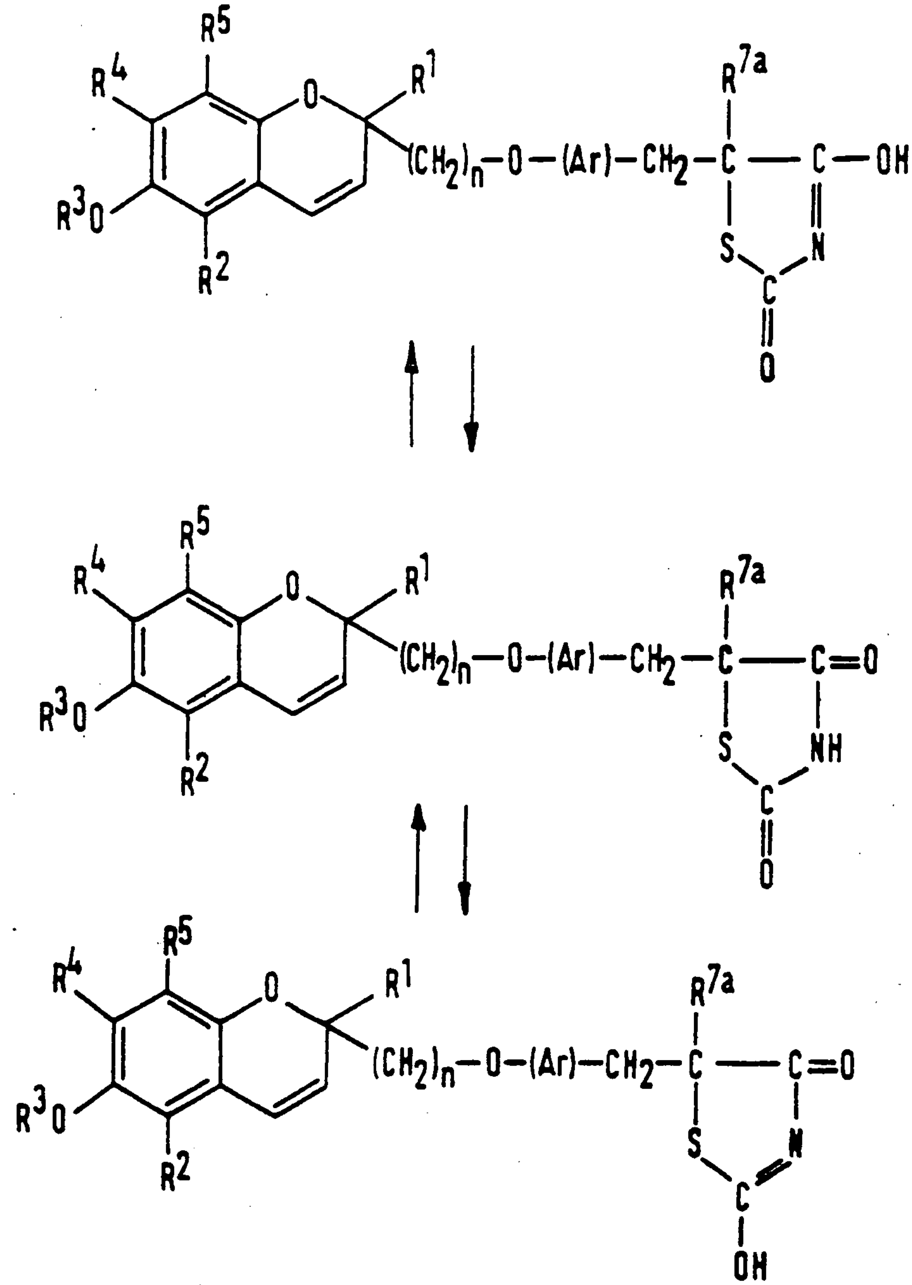
The nature of the reagents, solvent, proportions of reagents and reaction conditions such as temperature and reaction time, are as described above in relation to the acylation of a compound of formula (IVH) to give the corresponding ester. In view of this, depending upon the precise reaction conditions, where the compound of formula (VI) used as starting material is a compound in which R^3 represents a hydrogen atom, then that hydrogen atom may simultaneously be replaced by an acyl group to give a compound of formula (VIII) in which both R^3 and R^{11a} represent the same acyl group.

Compounds of the invention in which W and U together form a carbon-carbon double bond, that is to say compounds of formula (IX):



(IX)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n and Ar are as defined above) can be prepared by eliminating water from the above compound of formula (VI) or eliminating an acid $R^{11a}OH$ from the aforementioned compound of formula (VIII). The compounds of formula (IX) can exist in various tautomeric forms, as illustrated below:



Elimination of water or of the acid $R^{11a}OH$ from the compound of formula (VI) or (VIII) may be effected by contacting the compound with an acid catalyst in a solvent; alternatively, if an acidic solvent is employed, then no additional acid catalyst is required.

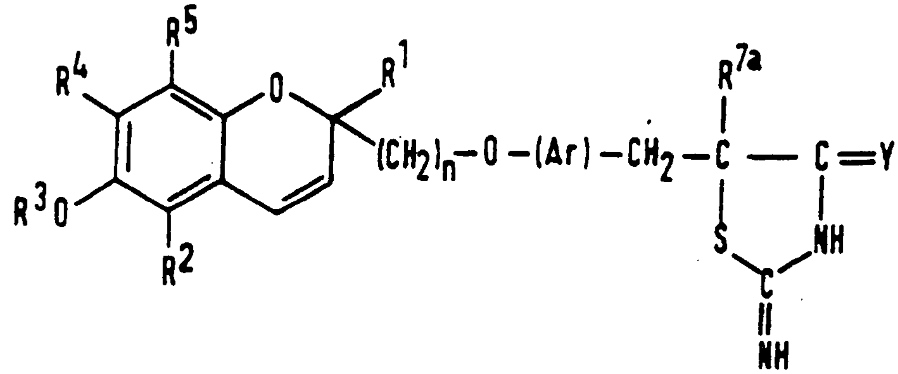
Suitable acid catalysts include: inorganic acids, such as hydrochloric acid or sulphuric acid; organic carboxylic acids, such as acetic acid; and organic sulphonic acids, such as p-toluenesulphonic acid. The nature of th solvent employed is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene or xylene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptane; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; ketones, such as acetone or methyl ethyl ketone; water; and mixtures of any two or more thereof.

There is no particular restriction on the ratio of the compound of formula (VI) or (VIII) to the acidic catalyst. However, we generally prefer to employ a molar ratio of said compound to said catalyst of from 1:0.001 to 1:1, more preferably from 1:0.01 to 1:0.1.

Where an acidic solvent is to be employed, we prefer to use an organic acid, particularly an organic carboxylic acid, such as acetic acid.

The reaction will take place over a wide range of temperatures, although we generally prefer to employ a temperature of from 0°C to 100°C. The time required for the reaction may vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature, but a period of from 5 minutes to 20 hours will normally suffice.

Compounds of formula (IX) may also be prepared by hydrolysis of the corresponding imino compound of formula (X):

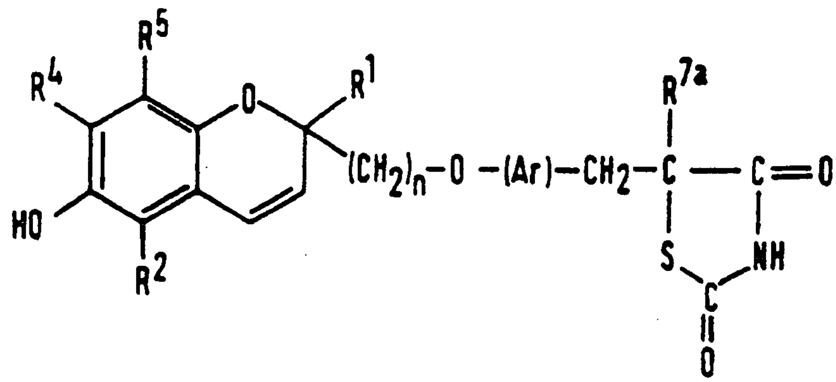


(X)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n and Ar are as defined above: and Y is also as defined above, i.e. it is an oxygen atom or an imino group).

The compound of formula (X) may be prepared from the compound of formula (V) by a series of reactions analogous to those employed to prepare the compound of formula (IX) from the compound of formula (VII), employing the same reagents and reaction conditions.

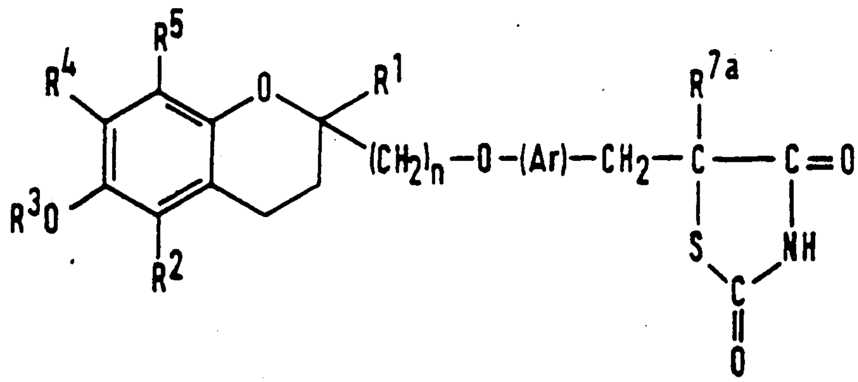
The hydrolysis reaction employed is the same as that employed to convert the compound of formula (V) into the compound of formula (IV) and may be carried out under the same conditions and employing the same reagents as described in the context of that reaction. As with that reaction, the hydrolysis in this reaction may lead to removal of any acyl group represented by R^3 and its replacement by a hydrogen atom, to give a compound of formula (IXH):



(IXH)

(in which R^1, R^2, R^4, R^5, R^{7a}, n and Ar are as defined above). However, the acyl group may be kept intact by selecting suitable r action conditi ns. Also, if desired, the acyl group may be reinstated by an acylation reaction, as described above in relation to acylation of the compound of formula (IVH).

Compounds of formula (I) in which W represents a methylene group, that is to say compounds of formula (XI):

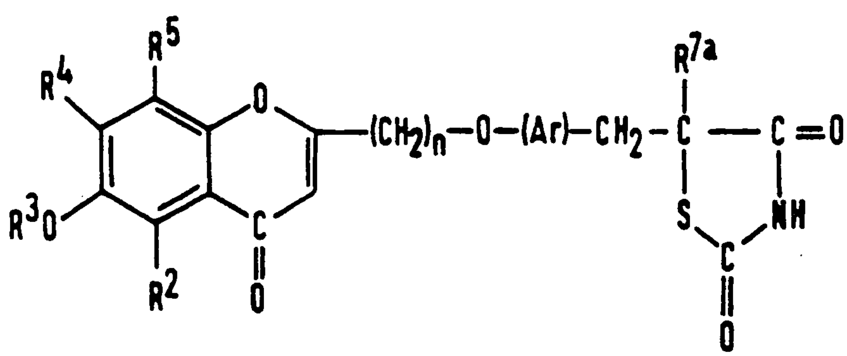


(XI)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n and Ar are as defined above), may be prepared by hydrogenation of a compound of formula (IX).

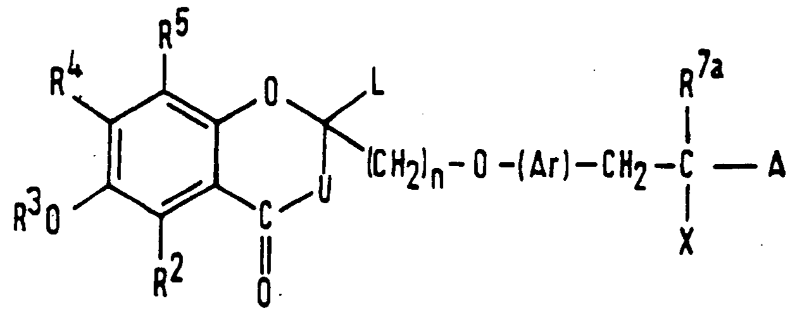
This hydrogenation is preferably effected in the presence of a catalyst, for example palladium-on-carbon, Raney nickel or platinum oxide, of which palladium-on-carbon is preferred. The partial pressure of hydrogen is preferably from 1 to 100 atmospheres (about 1 to 101 bars), more preferably from 1 to 6 atmospheres (about 1 to 6 bars). The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol or ethanol; aromatic hydrocarbons, such as benzene or toluene; ethers, such as tetrahydrofuran; organic acids, such as acetic acid; amides, such as dimethylformamide or dimethylacetamide; water; and mixtures of any two or more thereof. The reaction will take place over a wide range of temperatures, but we normally find it convenient to carry out the reaction at a temperature within the range from room temperature to 50°C. The time required for the reaction will vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature, but a period of from 5 minutes to 20 hours will normally suffice, where a temperature within the recommended range is employed.

Compounds of formula (I) in which W represents a carbonyl group and U, R^1 and the carbon atom to which R^1 is attached together represent a group of formula -CH=C<, that is to say a compound of formula (XII):



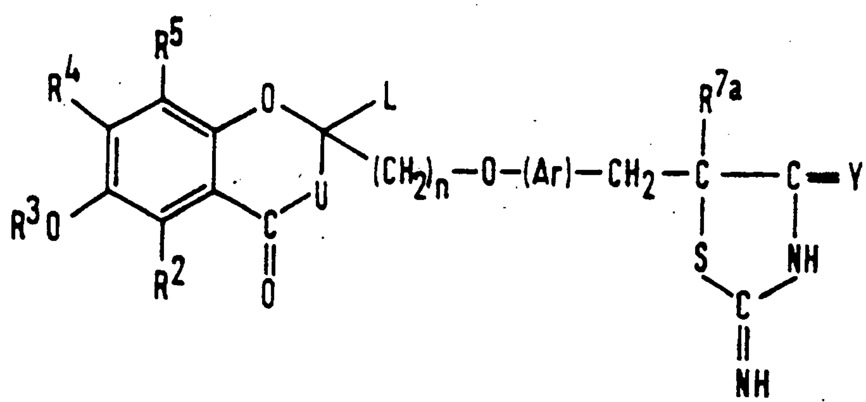
(XII)

(in which R², R³, R⁴, R⁵, R⁷ᵃ, n and Ar are as defined above), can be prepared by reacting a compound of formula (XIII):



(XIII)

(in which R², R³, R⁴, R⁵, R⁷ᵃ, A, X, n and Ar are as defined above and L and U are as defined below) with thriorea, to give a compound of formula (XIV):



(XIV)

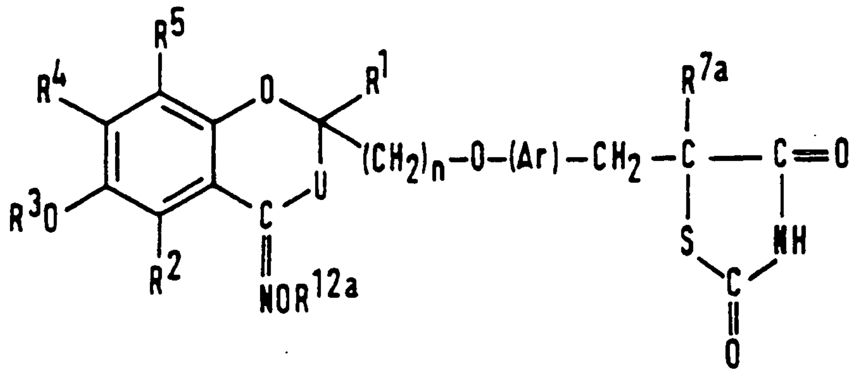
(in which R², R³, R⁴, R⁵, R⁷ᵃ, Y, n and Ar are as defined above and L and U are as defined below) and then hydrolizing this compound in the presence of an acid to give said compound of formula - (XII).

In the above formulae, L represents a group of formula -OR³, in which R³ is as defined above, and U represents a methylene group; alternatively, U, L and the carbon atom to which the group represented by L is attached together form a group of formula -CH=C<.

The reactions of the compound of formula (XIII) with thiourea and the hydrolysis of the compound of formula (XIV) thus produced to give the desired compound of formula (XII) are similar to the reactions of the compound of formula (II) with thiourea to give the compound of formula (V) and the hydrolysis of this to give the compound of formula (IV) and may be carried out employing the same reagents and under the same reaction conditions.

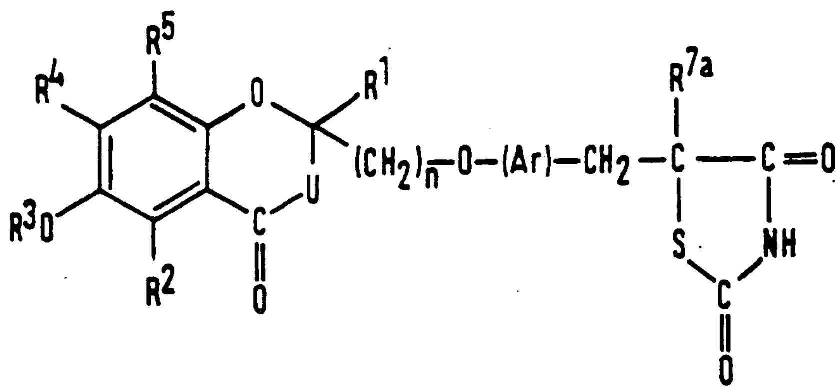
Compounds of formulae (X), (IXH), (XI), (XII) and (XIV) exist as tautomeric forms, analogous to those already described above in relation to compounds of formulae (IV), (VI), (VIII) and (IX), although all such tautomers are represented herein by a single formula only, for convenience.

Compounds of formula (I) in which W represents a group of formula >C=N-OR¹²ᵃ, that is to say compounds of formula (XV):



(XV)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, U, n and Ar are as defined above; and R^{12a} represents a hydrogen atom, a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group, as defined for R^{12}), can be prepared by reacting the corresponding compound in which W represents a carbonyl group, that is to say a compound of formula (XVI):



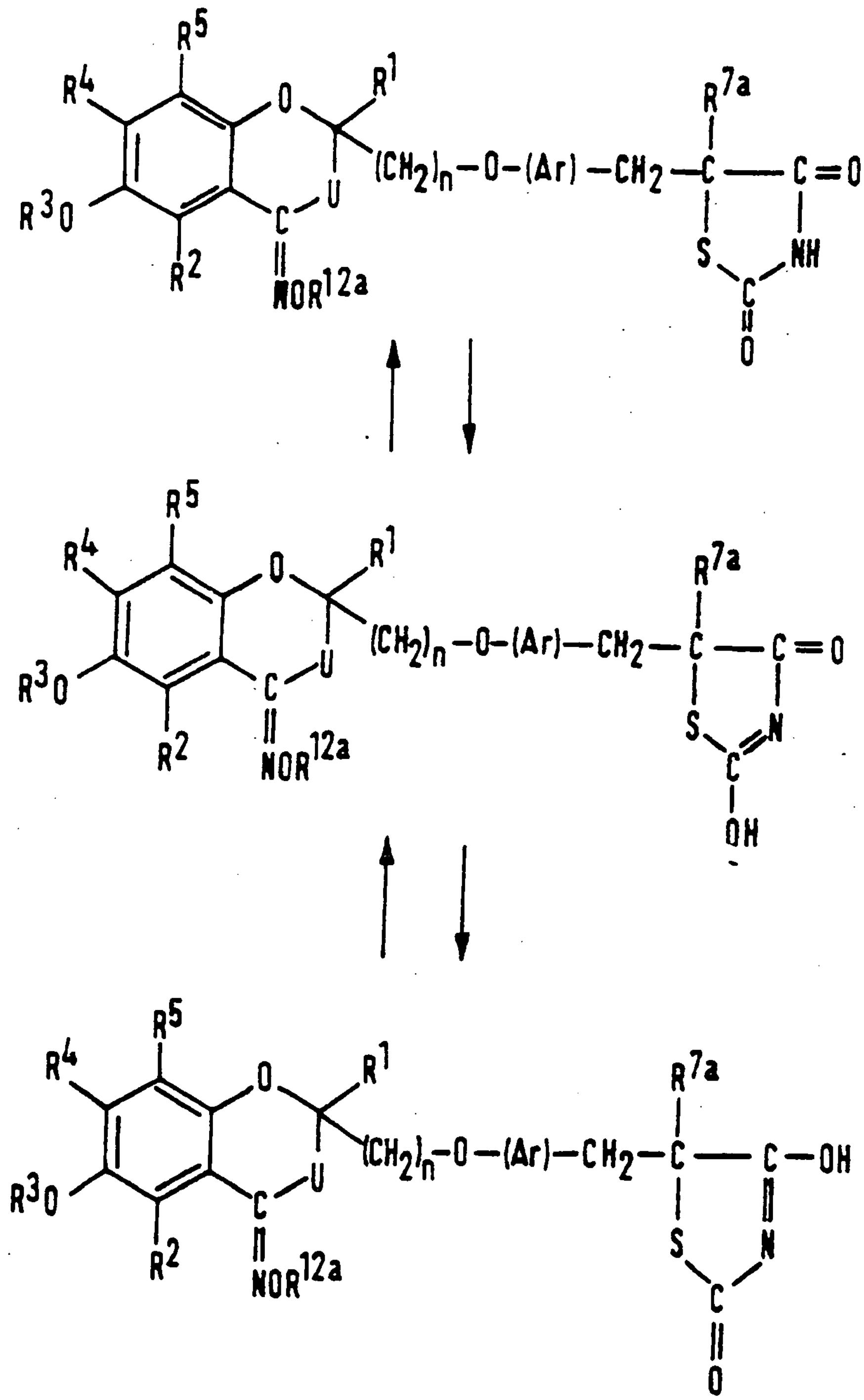
(XVI)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, U, n and Ar are as defined above) with a hydroxylamine derivative of formula (XVII):

H_2N-OR^{12a} (XVII)

(in which R^{12a} is as defined above) or a salt thereof.

The compounds of formulae (XV) and (XVI) can exist in tautomeric forms, for example as follows in relation to the compound of formula (XV):



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however, for convenience, these are represented herein by a single formula only.

The nature of the hydroxylamine derivative of formula (XVII) depends upon th natur of the group =NOR^{12a} which it is desired to introduce into the compound. The hydroxylamine derivative may be employed in the form of a salt thereof, for example a salt with a mineral acid, such as hydrochloric acid or sulphuric acid.

The reaction may be effected in the presence of an acid-binding agent. Where an acid-binding agent is employed, it is preferably an alkali metal hydroxide (such as potassium hydroxide) or an alkali metal carbonate (such as sodium carbonate or potassium carbonate).

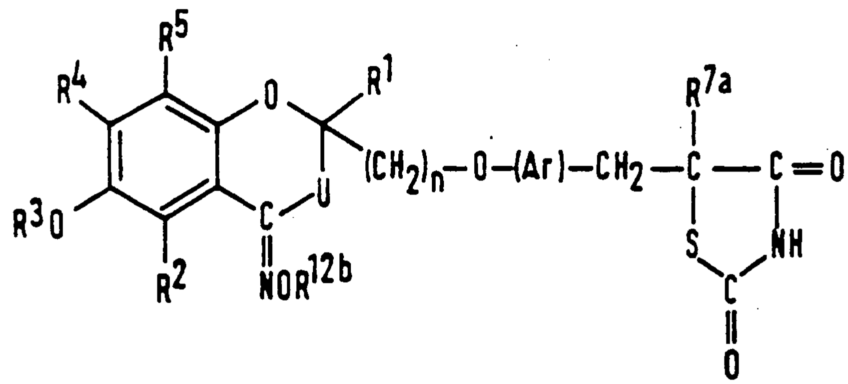
The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Examples of suitable solvents include: alcohols, such as methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether; ethers, such as tetrahydrofuran or dioxane; amides, such as dimethylformamide or dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; sulphones, such as sulpholane; organic bases, such as triethylamine or pyridine; water; and mixtures of any two or more thereof.

There is no particular limitation on the molar ratio of the hydroxylamine derivative of formula (XVII) to the compound of formula (XVI) and the reaction will take place at any molar ratio. However, we generally prefer to employ an excess of the hydroxylamine derivative, preferably a large excess, with respect to the compound of formula (XVI). A preferred molar ratio of the hydroxylamine derivative (XVII) to the compound of formula (XVI) is from 1:1 to 50:1.

If an acid addition salt of the hydroxylamine derivative (XVII) is employed, then we prefer to carry out the reaction in the presence of an acid-binding agent. The amount of acid-binding agent is not critical and an amount less than equimolar with respect to the salt of the hydroxylamine derivative can be employed.

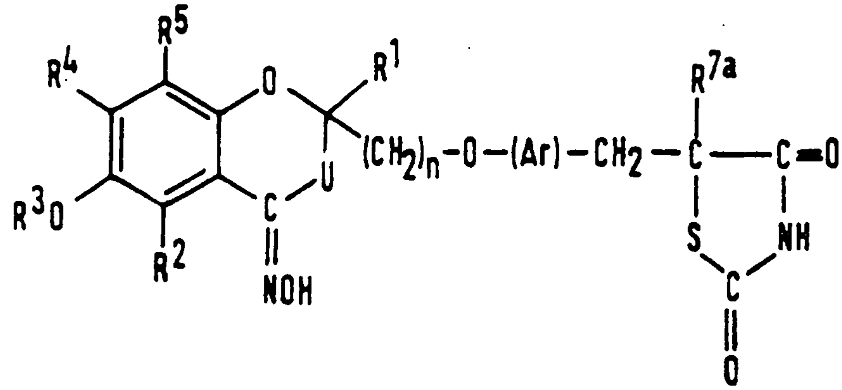
The reaction will take place over a wide range of temperatures and the particular temperature chosen is not critical. We prefer to carry out the reaction at a temperature within the range from 0°C to 100°C. The time required for the reaction will vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature, but, at temperatures within the preferred range given above, a period of from 5 minutes to 10 days will normally suffice.

Compounds of formula (I) in which W represents a group of formula >C=N-O-R^{12b} (in which R^{12b}represents any one of the acyl groups defined for R^{12}), that is to say compounds of formula (XVIII):



(XVIII)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, R^{12b}, U, n and Ar are as defined above), may be prepared by reacting the corresponding compound of formula (XV) in which R^{12a} represents a hydrogen atom, that is to say a compound of formula (XIX):



(XIX)

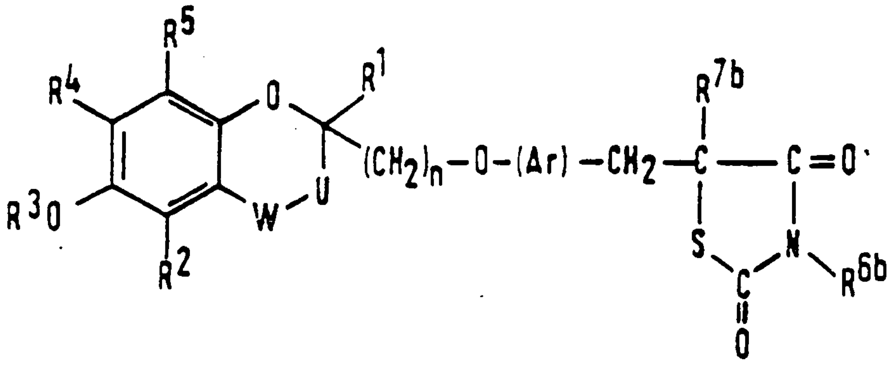
(in which R', R², R³, R⁴, R⁵, R⁷ᵃ, U, n and Ar are as defined above) with an acylating agent, preferably an acid halide or acid anhydride, especially an acid anhydride.

The compounds of formula (XVIII) can exist in the form of tautomers, analogous to those defined above in relation to the other similar compounds. However, for convenience, these tautomers are all represented herein by a single formula (XVIII).

The acylation reaction of this compound of formula (XIX) to give the compound of formula (XVIII) is essentially the same as the reaction employed to acylate the compound of formula (IVH) and may be carried out under the same conditions and employing the same reagents, solvents, etc. as described heretofore in relation to that acylation reaction.

The compounds of the invention in which W represents a group of formula >C=N-OR^{12} (in which R^{12} is as defined above), that is to say the oxime, oxime ether and oxime ester compounds, i.e. compounds of formulae (XV), (XVIII) and (XIX), can exist in both the syn and anti forms, and both forms are included within the scope of the present invention. These oxime, oxime ether and oxime ester compounds can be converted into their salts by conventional means. As with the salts described previously, there is no particular limitation on the nature of the salt, provided that, where the salt is to be employed for therapeutic purposes, it should be pharmaceutically acceptable. Suitable salts include: alkali metal salts, such as the sodium or potassium salt; alkaline earth metal salts, such as the calcium salt; and salts with trivalent metals, such as the aluminium salt. However, other salts, including those other ones described above can also be formed.

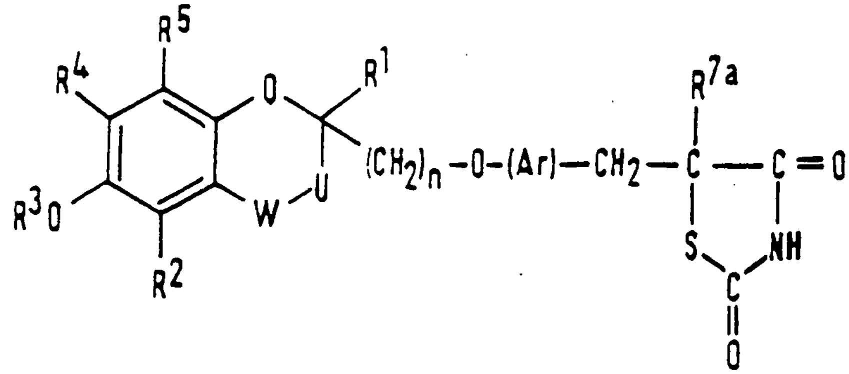
Compounds of the invention in which R⁶ and/or R⁷ represents an alkyl group or substituted alkyl group, i.e. compounds of formula (XX):



(XX)

(in which R', R², R³, R⁴, R⁵, W, U, n and Ar are as defined above; and

R^{6b} and R^{7b} ar the sam or different and each represents a hydrogen atom, a C_1-C_{10} alky group or a substituted C_1-C_{10} alkyl group, as defined in relation to R⁶ and R⁷, provided that R^{6b} and R^{7b} d not both represent hydrogen atoms), can be prepared by reacting a compound of formula (XXI):



(XXI)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, W, U, n and Ar are as defined above) with an alkyl halide or substituted alkyl halide of formula (XXII):

$R^{20}X$ (XXII)

(in which R^{20} represents R^{6b} or R^{7b} and X represents a halogen atom, for example a fluorine, chlorine, bromine or iodine atom, preferably a chlorine or bromine atom).

The reaction is preferably effected in the presence of an acid-binding agent. The purpose of the acid-binding agent is to remove from the reaction system the hydrogen halide HX produced by the reaction and any compound capable of doing this may be employed. Examples of suitable acid-binding agents include: alkali metal carbonates, such as sodium carbonate or potassium carbonate; alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide; alkali metal bicarbonates, such as sodium bicarbonate or potassium bicarbonate; alkaline earth metal hydroxides, such as calcium hydroxide; alkali metal hydrides, such as sodium hydride or potassium hydride; alkali metal alkoxides, such as sodium methoxide or sodium ethoxide; organic lithium compounds, such as butyllithium or t-butyllithium; lithium dialkylamides, such as lithium diisopropylamide or lithium dicyclohexylamide; and organic bases, such as pyridine or triethylamine. Of these, the alkali metal carbonates, especially potassium carbonate, are preferred.

The relative proportions of the base and the compound of formula (XXI) are not particularly critical and may vary over a wide range. For example, a molar ratio of base to compound (XXI) of from 0.5:1 to 20:1 is preferred, more preferably from 1:1 to 10:1.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: ketones, such as acetone or methyl ethyl ketone; ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene or xylene; aliphatic hydrocarbons, such as hexane, heptane or cyclohexane; amides, such as dimethylformamide or dimethylacetamide; sulphoxides, such as dimethyl sulphoxide, sulphones, such as sulpholane; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride, chloroform or 1,2-dichloroethane; organic bases, such as pyridine or triethylamine; water; and mixtures of any two or more thereof.

The molar ratio of the compound of formula - (XXI) to the alkyl halide of formula (XXII) is not particularly critical but, in order to ensure that the reaction goes to completion, we prefer to employ an excess of the alkyl halide. In general, the molar ratio of the alkyl halide to the compound of formula (XXI) is from 0.5:1 to 20:1, more preferably from 1:1 to 10:1. Where only a group R^{6b} is to be introduced into the compound, a still more preferred molar ratio is from 1:1 to 5:1, most preferably from 1:1 to 3:1. Where both groups R^{6b} and R^{7b} are to be introduced, the more preferred ratio is from 1:1 to 10:1 and the most preferred ratio is from 3:1 to 6:1.

The reaction will take place over a wide range of temperatures and the particular reaction temperature is not particularly critical. We generally prefer to carry out the reaction at a temperature of from -10°C to +100°C, more preferably from 15 to 40°C. The time required for the reaction may vary widely, depending upon many factors, notably the reaction t mperature and the nature of the

reagents, howev r, at a temperature within the preferred range, a period of from 10 minutes to several days, more commonly from 1 hour to 4 days, will normally suffice.

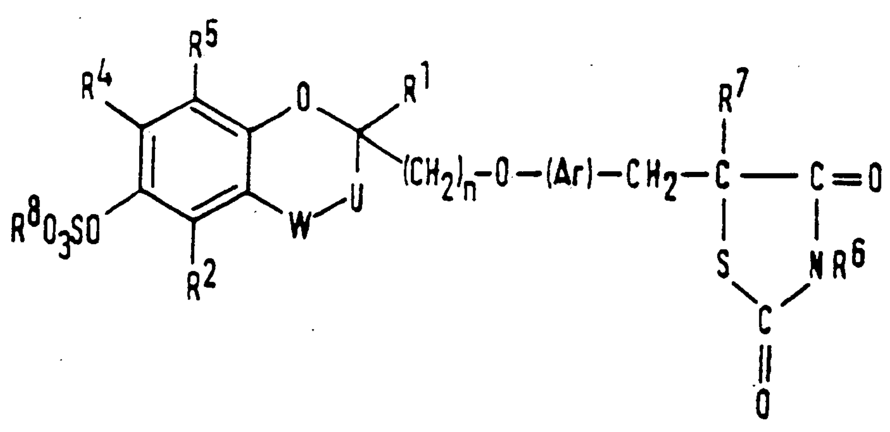
Where only R^{6b} is to be introduced, a preferred reaction temperature is from 0 to 100°C, more preferably from 15 to 40°C. At such a temperature, the reaction time will normally be from 10 minutes to several hours, commonly from 30 minutes to 3 hours.

Where both R^{6b} and R^{7b} are to be introduced, a preferred reaction temperature is from 0 to 100°C, more preferably from 15 to 40°C. At such a temperature, the reaction time will normally be from 10 minutes to several days, commonly from 5 hours to 2 days.

The reaction normally takes place preferentially at the nitrogen atom at the 3-position of the thiazolidine ring and, accordingly, where the quantity of alkyl halide (XXII) is restricted, the principal product will normally be a compound in which the alkyl or substituted alkyl group has been introduced at that position. Where R^{7a} represents a hydrogen atom in the compound of formula (XXI), it is possible to replace this by an alkyl or substituted alkyl group by this reaction and, provided sufficient alkyl halide (XXII) is employed, disubstitution will take place.

Where a compound in which R^6 and/or R^7 represents a carboxyalkyl group is required, we prefer to employ a compound of formula (XXII) in which R^{20} represents an alkoxycarbonylalkyl or substituted alkoxycarbonylalkyl group, to give the corresponding compound of formula (XX) where R^{6b} and/or R^{7b} represents that alkoxycarbonylalkyl or substituted alkoxycarbonylalkyl group. The resulting compound of formula (XX) may then be hydrolized to remove the alkoxy or substituted alkoxy part of this alkoxycarbonylalkyl group and give a free carboxyalkyl group. In general, particularly where W is $>CH_2$ or $>C=O$, the hydrolysis reaction employed is similar to the hydrolysis employed to convert the compound of formula (V) to a compound of formula (IV) and may be carried out under the same reaction conditions and employing the same reagents. In the case of lower alkyl, e.g. ethyl or t-butyl, esters, the free acid may be formed at a relatively low temperature, e.g. from 0 to 5°C, by treatment with an aqueous alkali, e.g. alkali metal hydroxide, such as sodium hydroxide. In the case of alkoxyalkyl esters, e.g. the 2-methoxyethyl esters, the reaction is preferably effected at a higher temperature in the presence of an acid. As with the previously described hydrolysis reaction, there is a possibility that the hydrolysis may also hydrolize any acyl group represented by R^3 in the compound of formula (XX) to give a compound - (XXI) in which R^3 represents a hydrogen atom. However, this may be avoided by appropriate choice of reagents and reaction conditions.

Compounds of the invention in which R^3 represents a sulpho (HSO_3-) group or an esterified sulpho group of formula $-SO_3R^8$, i.e. compounds of formula (XXIII):



(XXIII)

(in which R^1, R^2, R^4, R^5, R^6, R^7, R^8, W, U, n and Ar are as defined above), may be prepared by reacting the corresponding compound of formula (I) in which R^3 represents a hydrogen atom, e.g. a compound of formula (IVH) or (IXH), with a corresponding halosulphonic acid or halosulphonate of formula (XXIV):

XSO_2OR^8 (XXIV)

(in which R^8 and X are as defined above).

The reaction is similar to th reaction to introduce an alkyl or substituted alkyl group R^{6b} or R^{7b} into a compound of formula (XXI) and may be carried out und r the same conditions and empl ying the same solvents and acid-binding agents.

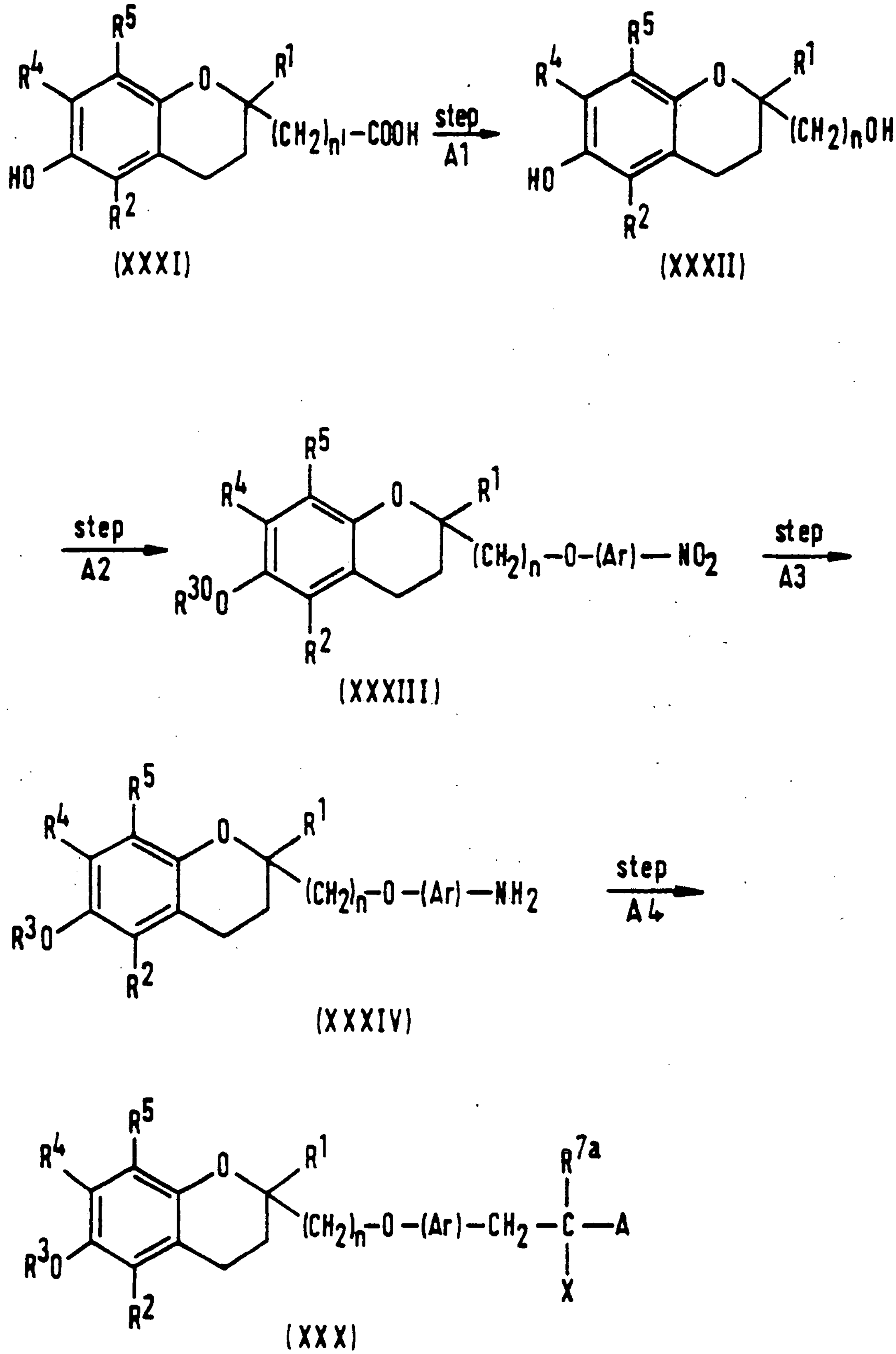
In all of th compounds of the invention, the carbon atom at the 5-position of the thiazolidine ring is asymmetric. Moreover, when R^1 represents an atom or a group (i.e. it does not, together with U, form a double bond), the carbon atom at the 2-position of the chroman ring is asymmetric. When W represents a group of formula >CH-OR'', then the carbon atom at the 4-position of the chroman ring is also asymmetric. It will, therefore, be appreciated that a variety of isomers of the compounds of the invention are possible, as a result of different configurations of substituent groups about these asymmetric carbon atoms. Although all such isomers are represented herein by a single formula only, the present invention envisages both the individual isolated isomers and mixtures thereof. The compounds of the invention may be produced in the form of individual isomers by using an isolated isomer as the starting material or by stereospecific synthesis techniques. Alternatively, the compounds may be produced as a mixture of such isomers, in which case th y may be employed in the form of such a mixture or the individual isomers may be s parated by conventional resolution techniques.

The compounds of the invention obtained by any of the reactions discussed above may be isolated and purified by conventional techniques, including any one or more of the following: concentration; evaporation of solvent under reduced pressure; extraction with a solvent; crystallization and recrystallization; solvent transfer; chromatography techniques, especially column chromatography and thin layer chromatography; and optical resolution.

The α-halocarboxylic acid derivatives of formula (II) employed as starting materials in the processes of the present invention can be prepared by a variety of methods, for example as follows.

Method A

Method A is the method described in more detail in copending European Patent Publication No. 0139421 and prepares compounds where W and U both represent methylene groups, that is to say compounds of formula (XXX), as illustrated in the following reaction scheme:


step A1
(XXXI)
(XXXII)
step A2
step A3
(XXXIII)
step A4
(XXXIV)
(XXX)

In the above formulae, R^1-R^5, R^{7a}, Ar, n, A and X are as defined above, $n' = (n-1)$; and R^{30} represents a hydroxy-protecting group.

Step A1

The chroman carboxylic acid homologues - (XXXI), which are the starting materials for this Method, may be prepared as described, for example, in the Journal of the American Oil Chemists Society, 51, 200 (1974).

These acids (XXXI) are reduced with a reducing agent, such as lithium aluminium hydride or Vitride [sodium bis(2-methoxyethoxy)aluminium hydride], to give the corresponding chroman alcohol homologue (XXXII). This reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it does not interfere with the reaction. Suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene or xylene; and aliphatic hydrocarbons, such as hexane, heptane, cyclohexane, petroleum ether, ligroin or ethylcyclohexane.

The ratio of the amount of acid (XXXI) to reducing agent is not particularly critical, but we generally prefer to use a slight molar excess of reducing agent. Preferably the amount of reducing agent is from 1 to 2 moles per mole of acid (XXXI). The reaction conditions, particularly the reaction temperature and time, will vary depending upon many factors, such as the nature of the starting material, the reducing agent and the solvent, but the reaction is generally carried out at a temperature of from 0 to 100°C. At such a temperature, a reaction period of from 10 minutes to 20 hours will normally suffice.

Alternatively, the chroman alcohol homologue - (XXXII) may be prepared by reacting a hydroquinone with a compound of formula (XXXV):

$$HO-CH_2-CH=C\begin{matrix} \diagup R^1 \\ \diagdown (CH_2)_n-OH \end{matrix} \qquad (XXXV)$$

(in which n and R^1 are as defined above), especially the compound of formula (XXXV) where R^1 represents a methyl group, in the presence of aluminium chloride, as described in West German Patent No. 3,010,504.

Step A2

The chroman alcohol homologues of formula - (XXXII) obtained in step A1 may be converted to the corresponding nitrophenoxyalkyl chroman compounds (XXXIII). However, before carrying out this reaction, we prefer that the phenolic hydroxy group should be protected by a hydroxy-protecting group R^{30}.

The nature of the hydroxy-protecting group is not critical and any such group commonly used in this type of reaction and compound may be employed. Suitable groups include: alkoxyalkyl groups, such as the methoxymethyl group; alkoxycarbonylalkyl groups, such as the ethoxycarbonylmethyl, t-butoxycarbonylmethyl, 1-methoxycarbonyl-1-methylethyl and 1-(t-butoxycarbonyl)-1-methylethyl groups; aralkyl groups, such as th benzyl group; the 2-tetrahydropyranyl group; and acyl groups, such as the acetyl or benzoyl groups. The alkoxyalkyl, alkoxycarbonylalkyl and 2-tetrahydropyranyl groups are preferred. The reaction is normally effected by contacting a compound $R^{30}X$ (in which R^{30} is as defined above and X represents a halogen atom, preferably a chlorine atom), such as methoxymethyl chloride, ethoxycarbonylmethyl bromide, 1-(t-butoxycarbonyl)-1-methylethyl bromide, benzoyl chloride or benzyl chloride, more preferably methoxymethyl chloride or benzoyl chloride, with the compound of formula (XXXII) in the presence of a base such as an alkali metal or alkaline earth metal hydride (e.g. sodium hydride or calcium hydride) or an alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide or potassium t-butoxide). The reaction is normally carried out in the presence of a solvent, for example: an ether, such as diethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon, such as benzene, toluene or xylene; an aliphatic hydrocarbon, such as hexane or heptane; an amide, such as dimethylformamide or dimethylacetamide; a sulphoxide, such as dimethyl sulphoxide; or a sulphone, such as sulpholane. There is no particular limitation on the molar ratio of compound (XXXII) to the compound $R^{30}X$. In general, we prefer to employ from about 0.8 to 1.2 mole of the compound $R^{30}X$ per mole of the compound (XXXII). The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, especially the natures of the starting

material, the compound $R^{30}X$ and the solvent, but we normally prefer a reaction temperature of from 0 to 50°C and a tim of from several minutes to several tens of minutes.

The protected chroman alcohol produced by this reaction can, if desired, be isolated and purified, but it may be, and preferably is, converted to the nitrophenoxyalkylchroman compound of formula (XXXIII) without intermediate isolation.

Conversion to the compound of formula - (XXXIII) is effected by reacting the protected compound (XXXII) with a halonitroaryl compound, e.g. a 4-or 3-halonitrobenzene, of formula X-(Ar)-NO_2 (in which X and Ar are as defined above) in the presence of a base, such as sodium hydride, in a solvent, such as dimethyl sulphoxide or dimethylformamide. The amount of halonitroaryl compound employed is preferably about 2 moles per mole of protected compound (XXXII). The reaction temperature is preferably from 30 to 100°C and the time required for the reaction is usually from several minutes to several hours.

Step A3

The nitro compound of formula (XXXIII) thus obtained is reduced in this step to the corresponding amino compound of formula (XXXIV). In the course of or before or after this reduction, the protecting group R^{30} may be allowed to remain as it is, be removed or be converted to another group - (particularly an acyl group, such as an acetyl or benzoyl group).

When deprotection of the compound (XXXIII) is desired, this can easily be achieved by reacting the compound (XXXIII) with a dilute aqueous acid (such as hydrochloric acid, sulphuric acid or nitric acid) to hydrolyse the protecting group. The reaction is normally carried out in the presence of a solvent, for example: an alcohol, such as methanol, ethanol or propanol; and ether, such as tetrahydrofuran or dioxane; a ketone, such as acetone or methyl ethyl ketone; an organic acid, such as acetic acid or propionic acid; dimethyl sulphoxide; dimethylformamide; or water. Of these, water or an organic acid is preferred. The amount of acid used for hydrolysis is preferably from 0.01 to 5 moles, more preferably from 0.01 to 1 mole, per mole of the compound (XXXIII). We prefer to carry out the reaction in the presence of a large molar excess of water or of acetic acid as the solvent. The reaction temperature is preferably from ambient temperature to 100°C and the time required for the reaction is normally from several minutes to about 20 hours.

If it is desired to convert the protecting group R^{30} to another group, particularly an acyl group, this may be achieved by acylation of the deprotected compound obtained as described above. The acylating agent may be an acid halide, such acetyl chloride or benzoyl chloride, or an acid anhydride, such as acetic anhydride. This reaction is preferably carried out in the presence of an organic amine (such as pyridine or triethylamine) or in the presence of an inorganic base (for example an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide, or an alkali metal carbonate or bicarbonate, such as sodium carbonate, potassium carbonate or sodium bicarbonate). The acylating reaction is preferably carried out in the presence of a solvent, for example: an aliphatic hydrocarbon, such as hexane, cyclohexane, heptane, ligroin or ethylcyclohexane; an aromatic hydrocarbon, such as benzene, toluene or xylene; an organic amine, such as pyridine or triethylamine; a ketone, such as acetone or methyl ethyl ketone; an amide, such as dimethylformamide; a sulphoxide, such as dimethyl sulphoxide; or water. The ratio of the amount of deprotected compound (XXXIII) to acylating agent is not particularly critical, however, a slight molar excess of acylating agent is usually preferred, for example from 1 to 1.5 moles of acylating agent per mole of deprotected compound (XXXIII). Where an organic amine is employed as the acid-binding agent, it may be employed in any amount from 1 mole to a large molar excess per mole of the compound of formula (XXXIII). Where an inorganic base is employed as the acid-binding agent, it is preferably employed in an amount of from 1 to 10 moles per mole of the compound of formula (XXXIII). The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, particularly the natures of the starting material and solvent employed, but the reaction is preferably effected at a temperature of from 0 to 100°C for a period of from several minutes to 20 hours.

The nitro compound of formula (XXXIII) (which may optionally have been subjected to any of the processes described above) is then reduced to the amino compound of formula (XXXIV). The reduction may be a catalytic reduction process employing hydrogen, or reduction with a metal (such as zinc or iron) and an acid (which may be a mineral acid such as hydrochloric acid or sulphuric acid or an organic acid such as acetic acid). Preferably a catalytic reduction process is employed. The catalyst employed for this catalytic reduction is preferably palladium-on-carbon, Raney nickel or platinum oxide, of which palladium-on-carbon is particularly preferred. The hydrogen pressure is preferably from 1 to 100 atmospheres (about 1 to 101 bars), more preferably from 1 to 6 atmospheres (about 1

to 6 bars). The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: alcohols, such as methanol or ethanol; aromatic hydrocarbons, such as benzene or tolu ne; ethers, such as tetrahydrofuran; organic acids, such as acetic acid; water; or mixtures of any two or more thereof. The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, particularly the nature of the starting material, the method employed for reduction and the solvent, but the reaction is normally effected at a temperature from ambient temperature to 50°C and the period required for the reaction is generally from several minutes to about 20 hours.

Step A4

The chroman derivative of formula (XXXIV), prepared as described in step A3 above, is diazotized and then subjected to a Meerwein arylation, to give the desired α-halocarboxylic acid compound of formula (XXX). The two reactions are preferably effected sequentially in the same reaction system.

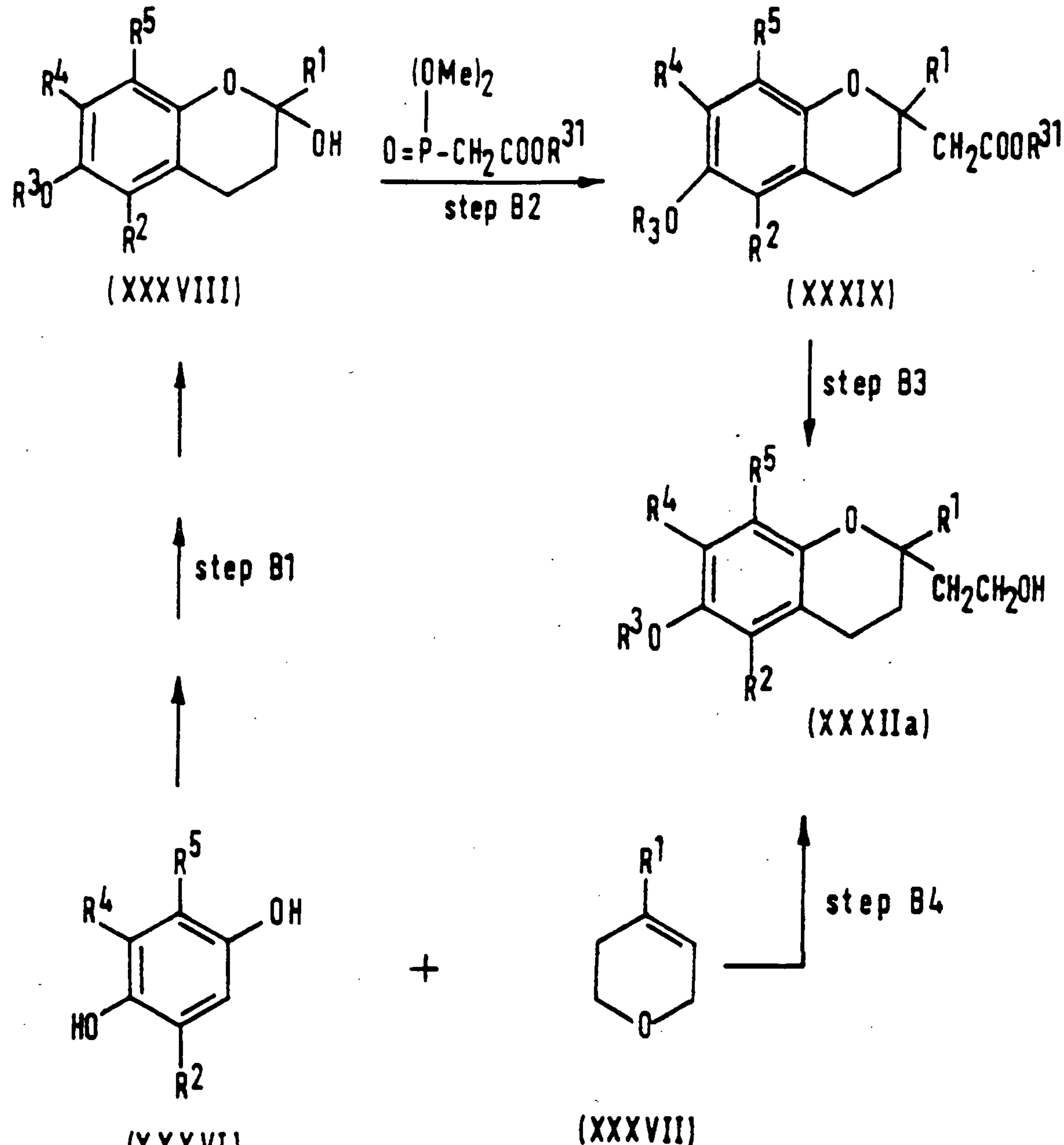
The diazotization reaction comprises reacting the amino compound of formula (XXXIV) with a nitrite (such as sodium nitrite) in the presence of an acid, such as hydrochloric acid or hydrobromic acid.

The Meerwein arylation reaction comprises reacting the resulting diazonium compound with an acrylic compound of formula $CH_2=CR^{7a}A$ (in which R^{7a} and A are as defined above), e.g. acrylic acid, an acrylic or methacrylic acid ester (such as methyl acrylate, ethyl acrylate or ethyl methacrylate) or another acrylic acid derivative (such as acrylonitril , acrylamide, methacrylonitrile or methacrylamide), in the presence of a catalytic amount of a cuprous compound (which may be a salt, such as cuprous chloride, or another cuprous compound such as cuprous oxide). The acrylic and methacrylic acid esters are preferred and the preferred cuprous compound is cuprous oxide.

The reactions are preferably effected in the presence of a solvent, the nature of which is not critical, provided that it does not interfere with the reactions. Suitable solvents include: alcohols, such as methanol or ethanol; ketones, such as acetone or methyl ethyl ketone; water; or a mixture of any two or more thereof. The molar ratio of the amino compound of formula (XXXIV) to the acrylic acid or derivative thereof of formula $CH_2=CR^{7a}A$ is preferably from 1:1 to 1:15, more preferably from 1:5 to 1:10. The molar ratio of the amino compound (XXXIV) to the cuprous compound is preferably from 1:0.01 to 1:1, more preferably from 1:0.03 to 1:0.3. The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, especially the natures of the starting materials and the solvent employed, but the reaction is normally carried out at a temperature from ambient temperature to 100°C, preferably from 30 to 60°C, and the period required for the reaction is normally from about 20 minutes to about 20 hours, more preferably from 30 minutes to 2 hours.

Method B

This method may also be used to prepare compounds of formula (II) in which both W and U represent methylene groups and is especially useful for preparing compounds in which n is 2. The reactions involved are illustrated in the following reaction scheme:

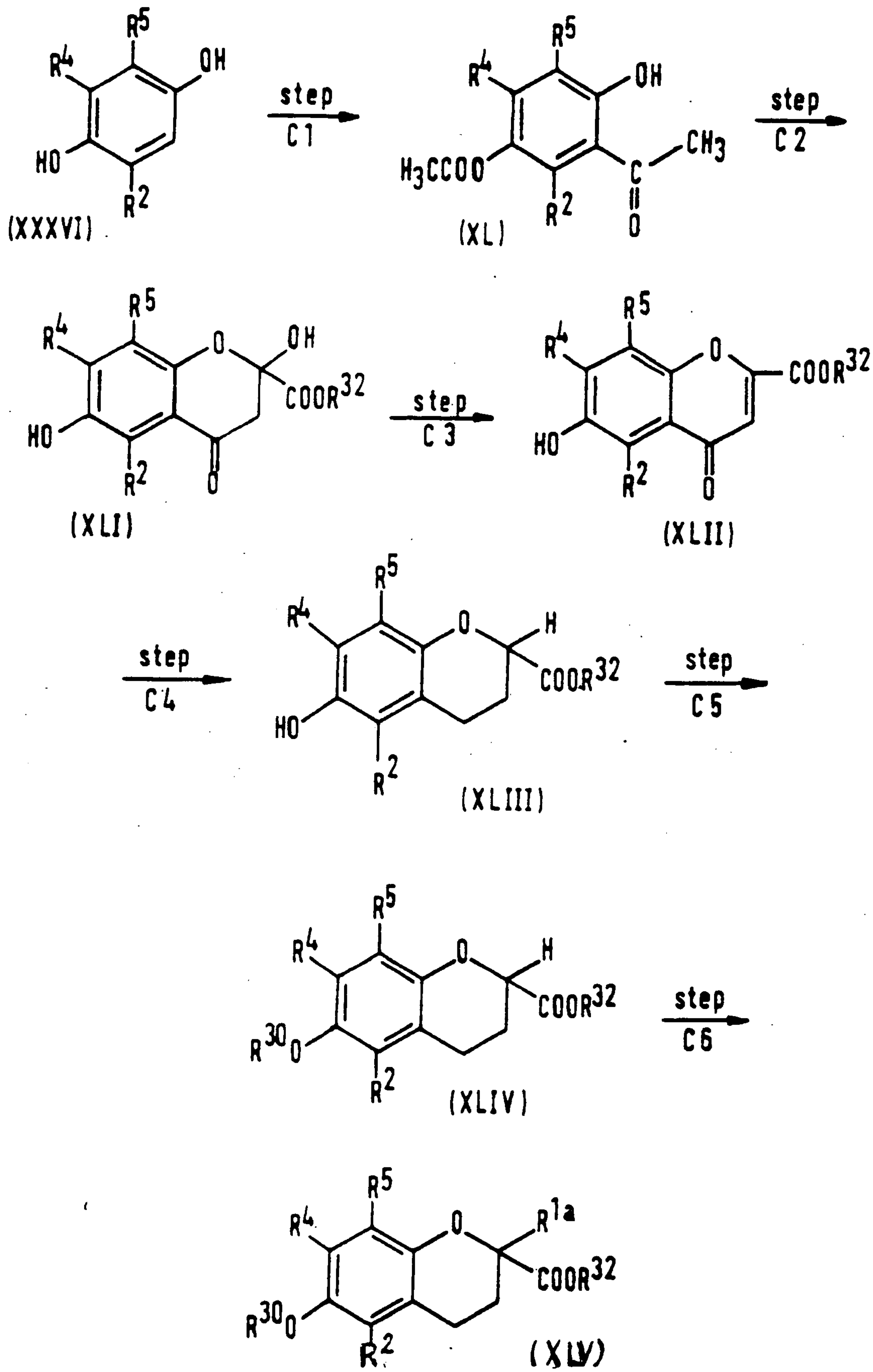


In the above reaction scheme, R¹-R⁵ are as defined above, R^{31} represents an alkyl group and Me represents the methyl group.

In this reaction, the chroman alcohol of formula (XXXIIa) or its analogues in which n is an integer other than 2, may be prepared from the hydroquinone derivative of formula (XXXVI) via the sequence of steps indicated as steps B1, to give the compound of formula (XXXVIII), followed by step B2, and then step B3 (analogous to step A1 of Method A), according to the method described in the Journal of the American Oil Chemists Society, 51, 200 (1974). Alternatively, it can be synthesized in a single step by reacting the hydroquinone derivative (XXXVI) with the dihydropyran derivative of formula (XXXVII), as illustrated in step B4 by the method described in Japanese Patent Application Kokai No. 201775/83. Subsequently, the resulting compound of formula (XXXIIa) may be subjected to steps A2, A3 and A4, to give the desired compound of formula (XXX).

Method C

This method is also useful for synthesizing compounds of formula (II) in which both W and U represent methylene groups. This method may be carried out as illustrated by the following reaction - scheme:



(XXXVI)
step C1
(XL)
step C2
(XLI)
step C3
(XLII)
step C4
(XLIII)
step C5
(XLIV)
step C6
(XLV)

In the above formulae, R^2, R^4, R^5 and R^{30} are as defined above; R^{1a} r presents any one of the groups heretofore defined for R^1, other than the hydrogen atom; and R^{32} represents a hydrogen atom or a carboxy-protecting group, preferably an alkyl, alkenyl, alkynyl, aralkyl or optionally substituted phenyl group, more preferably a C_1-C_4 alkyl group.

Steps C1-C4

These steps are carried out essentially as described in the Journal of Medicinal Chemistry, 18 ,934 (1975).

Step C5

In this step, the phenolic hydroxy group is, if required, protected. We prefer that this hydroxy group should be protected prior to step C6. Examples of protecting groups R^{30} have been given above in relation to Method A and the method of introducing the protecting group is also as described above in relation to step A2. However, in this step, we prefer to employ the compound $R^{30}X$ in excess, preferably a molar ratio of the compound $R^{30}X$ to the compound of formula (XLIII) of from 1:1 to 2:1. The reaction is preferably effected at a temperature of from 0 to 50°C, more preferably from 10 to 25°C. The time required for the reaction will vary, depending upon many factors, but a period of from several minutes to several hours will normally suffice. The resulting compound of formula (XLIV) may then be used in step C6 without intermediate isolation.

Step C6

In this step, a chromancarboxylic acid derivative of formula (XLV) having a protected hydroxy group at the 6-position and a group R^{1a} at the 2-position is prepared. This may be achieved by reacting the compound of formula (XLIV) with a base in an inert solvent in order to generate a carbanion and then reacting this carbanion with a compound of formula $R^{1a}X'$ (in which R^{1a} is as defined above and X' represents a halogen atom, for example a chlorine, bromine or iodine atom, or a sulphonyloxy group, for example a methanesulphonyloxy, ethanesulphonyloxy, benzenesulphonyloxy or p-toluenesulphonyloxy group).

Any base may be employed in the reaction to generate the carbanion, and examples of such bases include: organic lithium compounds, such as methyllithium, butyllithium, t-butyllithium or phenyllithium; lithium dialkylamides, such as lithium diisopropylamide, lithium dicyclohexylamide or lithium N-isopropyl-N-cyclohexylamide; and alkali metal hydrides, such as lithium hydride, sodium hydride or potassium hydride. Of these, we prefer the organic lithium compounds and lithium dialkylamides.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example, ethers, such as diethyl ether, tetrahydrofuran or dioxane.

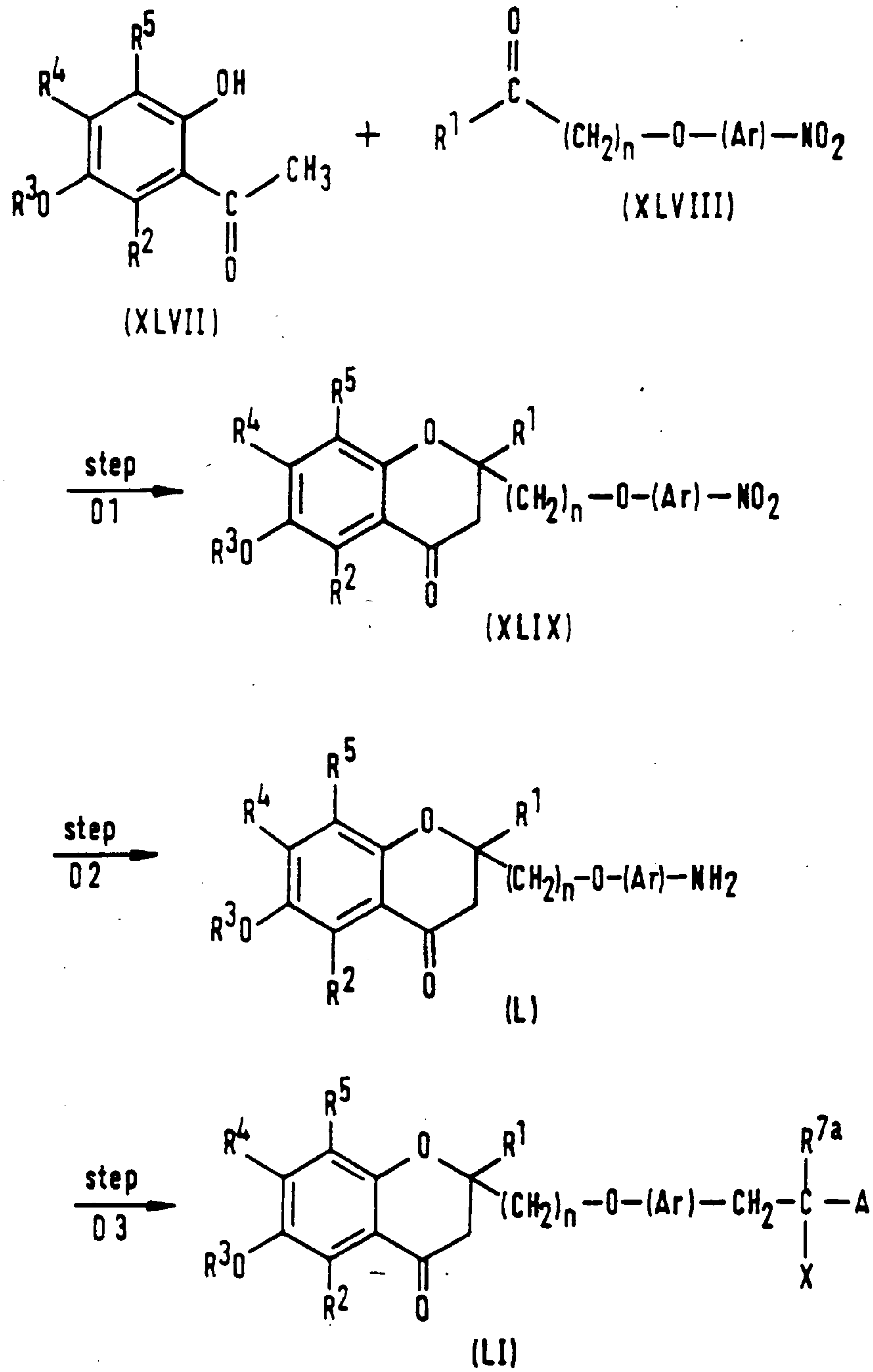
The reaction temperature employed for generation of the carbanion is preferably relatively low, e.g. from -78°C to room temperature. The temperature employed for reaction of this anion with the compound of formula R^{1a} X' is preferably somewhat higher, e.g. from 0°C to 60°C. The time required for these reactions will vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature, but a period of from 30 minutes to 2 hours will normally suffice for generation of the carbanion, whilst a period of from 1 to 24 hours will normally suffice for the subsequent reaction with the compound $R^{1a}X'$.

Thereafter, the resulting compound of formula - (XLV) may be subjected to the same reactions as described in Method A, to give the resulting compound of formula (XXX).

If desired, Step C6 may be omitted, to prepare a compound in which R^1 is a hydrogen atom.

Method D

This method is also described in copending European Patent Publication No. 0139421 and prepares compounds of formula (II) in which U represents a methylene group and W represents a carbonyl group, that is to say compounds of formula - (LI), by the reactions summarized in the following reaction scheme:


(XLVII)
(XLVIII)
step D1
(XLIX)
step D2
(L)
step D3
(LI)

In the abov formulae, R^1-R^5, R^{7a}, Ar, n, A and X are as defined above. The r action sequence comprises the following steps:

Step D1

The acetophenone derivative of formula - (XLVII) which is one of the starting materials for this step may be prepared, for example, as described in Chem. Berichte, 95, 1413. The other starting material, the nitroaryloxyalkyl alkyl ketone of formula (XLVIII), may be prepared, for example, as described in J. Med. Chem., 21, 386 (1978) and J. Am. Chem. Soc., 99, 7653 (1977).

In this step, the compounds (XLVII) and - (XLVIII) are reacted together in the presence of a secondary amine, as described, for example, in Japanese Patent Application Kokai No. 19670/77.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: aliphatic and aromatic hydrocarbons, such as petroleum ether, benzene, toluene, xylene, hexane and cyclohexane; halogenated aliphatic and aromatic hydrocarbons, such as carbon tetrachloride, methylene chloride, chloroform, chlorobenzene and dichlorobenzene; ethers, such as diethyl ether, tetrahydrofuran and dioxane; amides, such as dimethylformamide, dimethylacetamide and N-methylpyrrolidone; alcohols, such as methanol, ethanol and ethylene glycol monomethyl ether; esters, such as ethyl acetate; nitriles, such as acetonitrile; and sulphoxides, such as dimethyl sulphoxide.

The secondary amine employed in this reaction is preferably a compound of formula R^a-NH-R^b, in which R^a and R^b may the same or different and each represents an alkyl group, or R^a and R^b, together with the nitrogen atom to which they are attached, represent a nitrogen-containing heterocyclic ring system. Examples of such secondary amines include diethylamine, dimethylamine, N-methylpiperazine, pyrrolidine, piperidine or morpholine, of which pyrrolidine is particularly preferred.

The molar ratio of th compound of formula - (XLVII) to the compound of formula (XLVIII) is not particularly critical, but, to avoid waste, roughly equimolar amounts of the two compounds are used. In general, the amount of secondary amine is preferably from 0.05 to 1.5 moles, more preferably from 0.1 to 1 mole, per mole of the compound of formula (XLVII) or (XLVIII).

The reaction conditions, particularly reaction temperature and time, may vary depending upon a number of factors, especially the nature of the starting materials and of the solvent, but, in general, we prefer to carry out the reaction at a temperature of from -30°C to +150°C, more preferably from 10 to 120°C, for a period of from 30 minutes to 3 days.

Step D2

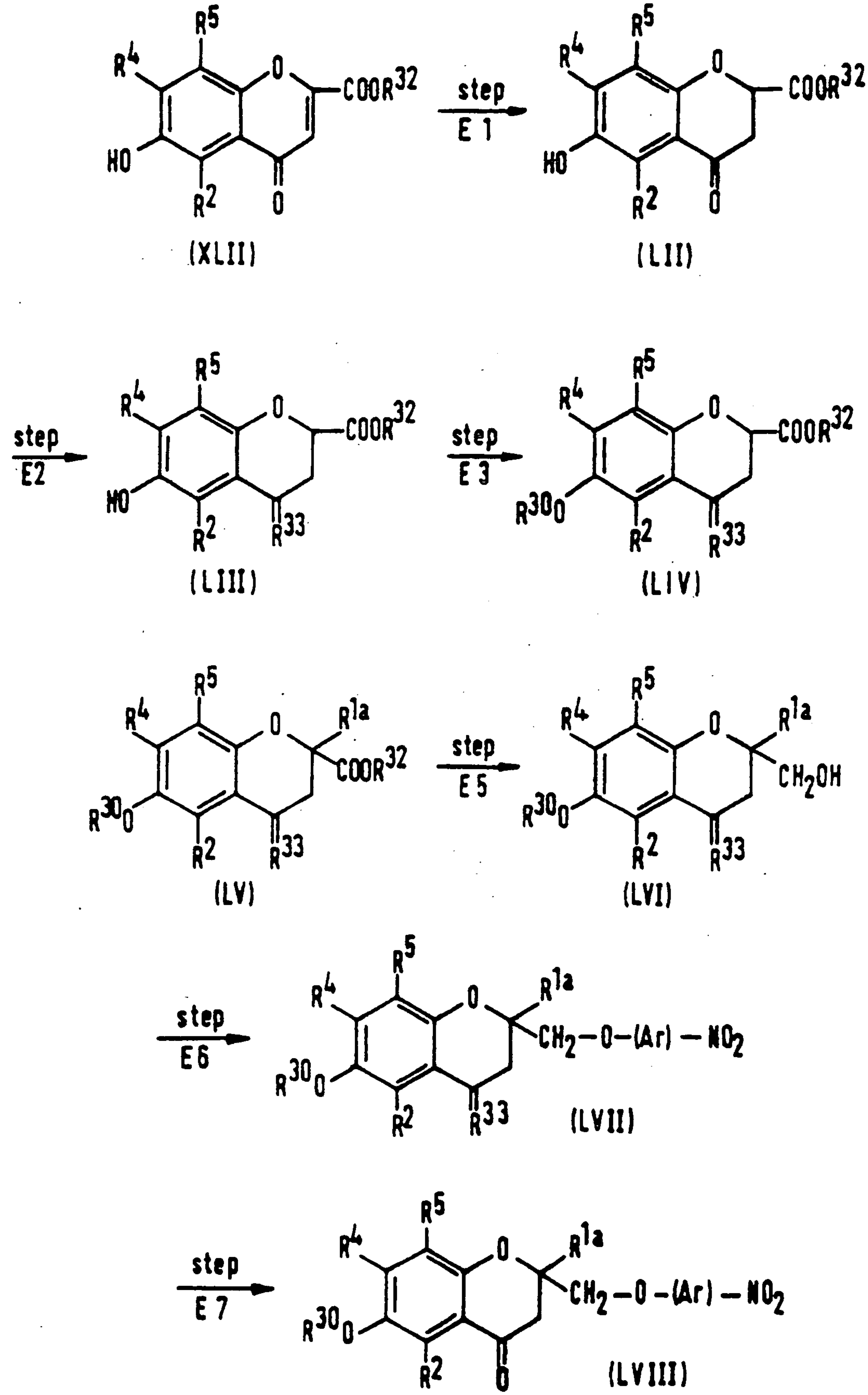
In this step, the nitro compound of formula - (XLIX) prepared as in step D1 is reduced to the corresponding amino compound of formula (L). This reaction is precisely the same as step A3 of Method A, employing the same reaction conditions and reagents.

Step D3

In this step, the amino compound of formula - (L), obtained as described in step D2, is diazotized and then subjected to a Meerwein arylation, to give the desired α-halocarboxylic acid derivative of formula (LI). These reactions are precisely the same as those described in step A4 of Method A and may be carried out employing the same reagents and reaction conditions.

Method E

This method may be used for preparing compounds of formula (II) in which W represents a carbonyl group and U represents a methylene group, and where there is a group R^{1a} (as defined above) at the 2-position of the chroman ring, that is to say compounds of formula (LVIII). The reactions involved are summarized in the following reaction - scheme:



(XLII) (LII) (LIII) (LIV) (LV) (LVI) (LVII) (LVIII)

In the above formulae, R^{1a}, R^2, R^4, R^5, R^{20}, R^{22} and Ar are as d fined abov . R^{23} repr sents a carbonyl-protecting group, examples of which are described in more detail below.

Step E1

In this step, the starting material of formula -(XLII), which may have been prepared as described in step C3 of Method C, is subjected to reduction, but under milder conditions than employed in step C4, so that only the double bond between the 2- and 3-positions is hydrogenated.

The reaction is preferably effected by catalytic hydrogenation. Suitable catalysts include palladium-on-carbon, Raney nickel and platinum oxide, of which palladium-on-carbon is preferred. The reaction is preferably effected employing a partial pressure of hydrogen of from 1 to 100 atmospheres (about 1 to 101 bars), more preferably from 1 to 6 atmospheres (about 1 to 6 bars). The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol or ethanol; aromatic hydrocarbons, such as benzene or toluene; ethers, such as tetrahydrofuran; amides, such as dimethylformamide or dimethylacetamide; organic carboxylic acids, such as acetic acid; water; and mixtures of any two or more thereof.

The reaction will take place over a wide range of temperatures, but we prefer to employ a temperature of from room temperatures to 50°C, more preferably from room temperature to 40°C. The time required for the reaction will vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature; however, at a temperature within the preferred range described above, the reaction will normally be complete within a period of from several minutes to several days, commonly from 30 minutes to 20 hours.

Step E2

In this step, the carbonyl group at the 4-position of the chroman compound of formula (LII) prepared in step E1 is protected; it is desirable that this protection should be carried out prior to the alkylation reaction of step E4.

There is no particular limitation on the nature of the protecting group employed and any such group commonly used for protecting carbonyl groups may equally w ll be used in th present invention. For example, the oxo compound may be converted into a protected enol compound, such as an enol eth r or enol est r. Alternativ ly, it may be converted into a ketone acetal having cyclic or noncyclic side chains or into a ketone dithioacetal. Conversion into a ketone dithioacetal is preferred.

Preferably, R^{23} represents a group of formula $-B^1-B^2-B^1-$, where B^1 represents an oxygen or sulphur atom (preferably a sulphur atom) and B^2 represents a group of formula $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$or $-CH_2-CH=CH-CH_2-$(cis), preferably $-(CH_2)_2-$or $-(CH_2)_3-$and more preferably $-(CH_2)_3-$. Such a protected compound may be prepared by reacting the compound of formula (LII) with a compound of formula $H-B^1-B^2-B^1-H$ (in which B^1 and B^2 are as defined above), for example ethylene glycol, 1,3-propanediol, 1,2-ethanedithiol, 1,3-propanedithiol or cis-2-butene-1,4-diol, preferably 1,3-propanedithiol, under dehydrating conditions. Th reaction may take place in the presence or absence of a catalyst. Where a catalyst is employed, suitable catalysts include, for example: Lewis acids, such as boron trifluoride (or diethyl ether or acetic acid complexes thereof) or aluminium chloride; inorganic acids, such as hydrogen chloride or sulphuric acid; organic carboxylic acids, such as acetic acid, tartaric acid, fumaric acid or maleic acid; and organic sulphonic acids, such as p-toluenesulphonic acid or methanesulphonic acid. We prefer to use a Lewis acid, more preferably a boron trifluoride acetic acid complex salt.

The reaction does not always require a solvent; however, if a solvent is employed, its nature is not critical, provided that it has no adverse effect upon the reaction. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene or xylene; and halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as chloroform or methylene chloride. Of these, we prefer halogenated hydrocarbons, such as chloroform.

There is no particular limitation on the proportions of the compound of formula (LII) to the compound of formula $H-B^1-B^2-B^1-H$; however, a small excess of the compound $H-B^1-B^2-B^1-H$ is preferred, preferably a molar ratio of the compound $H-B^1-B^2-B^1-H$ to the compound of formula (LII) of from 1:1 to 2:1. Equally, there is no particular limitation on the proportions of catalyst employed. However, a molar ratio of catalyst to compound of formula (LII) of from 1:1 to 1:4 is preferred.

The reaction will take place over a wide range of temperatures, but we generally prefer to carry out the reaction at a temperature of from 0 to 100°C, more preferably from 10°C to 40°C. The time required for the reaction may vary widely, depending upon the nature of the reagents and the reaction temperature, but a period of from several minutes to several days, more commonly from 1 hour to 30 hours, will normally suffice.

Step E3

In this step, the phenolic hydroxy group at the 6-position of the chroman ring is protected, typically by reaction with a compound of formula $R^{3a}X$ - (in which R^{3a} and X are as defined above). This reaction is similar to the reactions described in steps A2 and C5 and is preferably carried out employing the same reagents and under the reaction conditions described in relation to step C5. The resulting compound of formula (LIV) may be isolated from the reaction mixture or may be used without intermediate isolation directly in step E4.

Step E4

In this step, the compound of formula (LIV) is converted to a carbanion and then reacted with a compound of formula $R^{1a}X^1$ (in which R^{1a} and X^1 are as defined above). This reaction is similar to that described above in relation to step C6 and may be carried out employing the same reagents and under the same reaction conditions as employed in step C6.

If it is desired to prepare a compound in which R^1 represents a hydrogen atom, step E4 may be omitted, and the product of step E3 -the compound of formula (LIV) -may be employed directly in step E5.

Step E5

In this step, the chroman-2-carboxylic acid derivative of formula (LV) is reduced to the corresponding alcohol of formula (LVI). This reaction is essentially the same as that described above in step A1 of the Method A and may be carried out under the same conditions and employing the same reagents. However, in this case, we prefer to employ a temperature within the range from -50°C to +120°C.

Step E6

In this step, a group of formula -(Ar)-NO_2 (Ar being as defined above) is introduced into the compound of formula (LVI) prepared as described in step E5. This reaction may be effected by reacting the compound of formula (LVI) with a base to convert it to the corresponding alkoxide, and then reacting this with a compound of formula X-(Ar)-NO_2 (in which X and Ar are as defined above).

Any base capable of forming an alkoxide with the compound of formula (LVI) may be employed. Examples include: alkali metal and alkaline earth metal hydrides, such as sodium hydride or calcium hydride; and alkali metal alkoxides, such as sodium methoxide, sodium ethoxide or potassium t-butoxide. Of these, we prefer sodium hydride or sodium ethoxide. The proportions of the compound of formula (LVI) and the base are not particularly critical; however, we prefer to employ a slight excess of the base, preferably a molar ratio of base to compound of formula (LVI) of from 1:1 to 2:1.

The reactions are preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene or xylene; aliphatic hydrocarbons, such as hexane or heptane; amides, such as dimethylformamide or dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; and sulphones, such as sulpholane. Of these, the amides are preferred.

The relative proportions of the compound of formula X-(Ar)-NO_2 to the compound of formula - (LVI) are not particularly critical to the present invention, however, we prefer to employ a slight excess of the compound of formula X-(Ar)-NO_2, preferably a molar ratio of said compound of formula X-(Ar)-NO_2 to compound of formula (LVI) of from 1:1 to 10:1.

The reaction will take place over a wide range of temperatures, but we generally prefer to employ a temperature of from 30°C to 100°C. The time required for the reaction may vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature. A period of from several minutes to several hours will normally suffice.

The nitro compound of formula (LVII) thus obtained may then be converted to the desired compound of formula (XXX) by following steps A3 and A4 as described in Method A. At some stage in the course of this, the protected carbonyl group at the 4-position of the chroman system is deprotected and this may be carried out as described hereafter in step E7.

Step E7

In this step, the protected carbonyl group is deprotected. Any conventional reaction employed to deprotect a protected carbonyl group may be employed in this step. For example, the protected compound may be reacted with: a protonic acid, such as hydrochloric acid or sulphuric acid; a Lewis acid, such as boron trifluoride (or an ether, e.g. diethyl ether, or acetic acid complex thereof) or aluminium chloride; when B^1 represents a sulphur atom, a heavy metal salt, heavy metal oxide, heavy metal peroxide or a mixture of any two or three of these, for xample a silver, cadmium, mercurous, mercuric, cuprous or thallic chloride, bromide, iodide, nitrate, perchlorate, oxide or peroxide; iodine;

a sulphuryl halide, such as sulphuryl chloride; or an N-haloimide, such as N-chlorosuccinimide or N-bromosuccinimide. Of these, we pref r mercuric chl ride, mercuric oxide or a mixture thereof, more pr ferably a mixture of mercuric chloride and mercuric oxide.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol, ethanol, propanol or isopropanol; ketones, such as acetone or methyl ethyl ketone; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as chloroform, methylene chloride or 1,2-dichloroethane; ethers, such as tetrahydrofuran or dioxane; organic carboxylic acids, such as acetic acid; nitriles, such as acetonitrile; water; and mixtures of any two or more thereof.

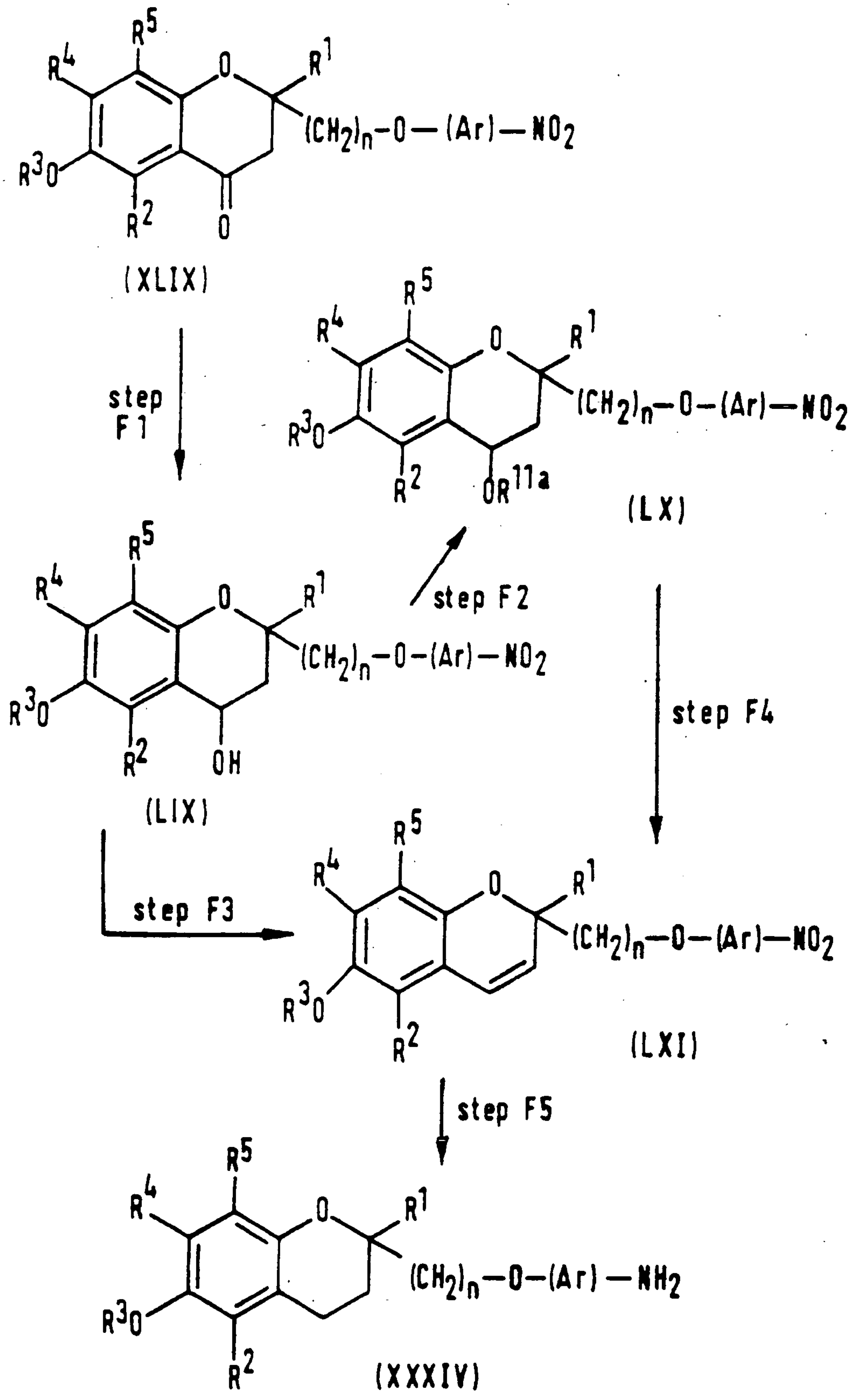
The proportions of the compound of formula (LVII) or other protected compound to the deprotecting agent are not critical. However, we prefer to employ a slight excess of the deprotecting agent, e.g. a molar ratio of deprotecting agent to compound of formula (LII) or other protected compound of from 1:1 to 10:1, more preferably from 1:1 to 4:1.

The reaction will tak place over a wide range of temperatures, but we generally find it convenient to carry out the reaction at a temperature within the range from room temperature to 100°C, more preferably from 40°C to 80°C. The time required for the reaction will vary, depending upon many factors, notably the nature of the reagents and the reaction temperature; however, at a temperature within the ranges mentioned above, a period of from several minutes to several hours, more commonly from 30 minutes to 4 hours, will normally suffice.

Thereafter, the compound of formula (LVIII) may be subjected to steps A3 and A4 to give the desired compound of formula (XXX). Alternatively, the deprotection step E7 may take place after or between these steps A3 and A4.

Method F

A particularly preferred process for preparing compounds of formula (II) in which both W and U represent methylene groups includes the steps illustrated in the following reaction scheme:


(XLIX)
step F1
(LX)
step F2
step F4
(LIX)
step F3
(LXI)
step F5
(XXXIV)

In the above formulae, R^1-R^6, n and Ar are as defined above and R^{11a} represents any one of the acyl groups defined above in relation to R^{11}.

Step F1

In this step, a 4-oxochroman derivative of formula (XLIX), which may have been prepared by a variety of the methods described above, including, for example step E7 of Method E or step D1 of Method D, is reduced to the corresponding 4-hydroxy compound of formula (LIX). Any reducing agent capable of reducing an oxo group on a saturated ring system to a hydroxy group may be employed. We generally prefer to employ sodium borohydride or K-selectride, of which sodium borohydride is particularly preferred.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether; and ethers, such as tetrahydrofuran or dioxane.

There is no particular limitation on the relative proportions of the compound of formula (XLIX) to the reducing agent, e.g. sodium borohydride, but we generally prefer to employ an excess, preferably a slight excess, of the reducing agent. In general, we would use a molar ratio of reducing agent to compound of formula (XLIX) of from 1:1 to 20:1.

The reaction will take place over a wide range of temperatures and the exact temperature chosen is not particularly critical. A temperature within the range from 0°C to 100°C is generally preferred. The time required for the reaction may vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature. However, a period of from 1 to 20 hours will normally suffice.

Step F2

In this optional step, the compound of formula (LIX) prepared as described in step F1 is acylated. The acylating agent employed is preferably an acid halide or acid anhydride.

The reaction is preferably carried out in the presence of a solvent, the nature of which is not critical, provided that it does not interfere with the reaction. Suitable solvents include, for example: ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluen or xylen ; aliphatic hydrocarbons, such as hexan , cyclohexane or heptan ; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; organic bases, such as pyridine or triethylamine; amides, such as dimethylformamide or dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; and sulphones, such as sulpholane.

There is no particular limitation on the proportions of compound of formula (LIX) to the acylating agent, but we generally prefer to use equimolar amounts or a slight excess of acylating agent. In general, a molar ratio of acylating agent to compound of formula (LIX) of from 1:1 to 10:1 is preferred. Where R^3 in the compound of formula (LIX) is a hydrogen atom, the group R^3O may also be acylated in the course of this reaction.

The reaction will take place over a wide range of temperatures and the particular temperature chosen is not critical. We generally prefer to carry out the acylation reaction at a temperature within the range from 0°C to 100°C. The time required for the reaction may vary over a wide range, depending upon many factors, notably the nature of the reagents and the reaction temperature; however, at a temperature within the preferred range, a period of from 5 minutes to 20 hours will normally suffice.

Step F3

In this step, which is an alternative to step F2, a 2H-chromene compound of formula (LXI) is prepared by dehydrating the 4-hydroxychroman (LIX).

The dehydration reaction may be achieved in the presence or absence of a dehydrating agent or dehydrating catalyst. Suitable dehydrating agents and catalysts include, for example: inorganic acids, such as hydrochloric acid, sulphuric acid, nitric acid or phosphoric acid; organic carboxylic acids, such as acetic acid, tartaric acid or maleic acid; organic sulphonic acids, such as p-toluenesulphonic acid, naphthalenesulphonic acid or methanesulphonic acid; inorganic salts, such as ammonium chloride or calcium chloride; phosphorus pentoxide; polyphosphoric acid; silica gel; and alumina. Of these, we prefer an organic carboxylic acid such as acetic acid or an organic sulphonic acid, such as p-toluenesulphonic acid.

It is not always necessary to employ a solvent in this reaction; however, where a solvent is used, its nature is not particular critical, provided that it does not interfere with the reaction. Examples of suitable solvents include: alcohols, such as methanol, ethanol or isopropanol; ketones, such as acetone or methyl ethyl ketone; ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene or xylene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptan ; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; organic carbox-

ylic acids, such as acetic acid or propionic acid; organic bases, such as pyridine or triethylamine; amides, such as dimethylformamide or dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; sulphones, such as sulpholane; water; and mixtures of any two or more thereof. Of these, we prefer aromatic hydrocarbons, such as benzene, or organic acids, such as acetic acid.

If a dehydrating agent or catalyst is employed, the relative proportion of such agent or catalyst to the compound of formula (LIX) is not critical, but we prefer to employ a molar ratio of said agent or catalyst to said compound of formula (LIX) of from 0.01:1 to 10:1, more preferably from 0.1:1 to 3:1.

The reaction will take place over a wide range of temperatures and the exact temperature chosen is not particularly critical; however, we generally prefer to carry out the reaction at a temperature in the range from 0°C to 100°C. The time required for the reaction will vary, depending upon many factors, notably the nature of the reagents and the reaction temperature; however, at temperatures within the preferred range indicated above, a period of from several minutes to 20 hours will normally suffice.

Step F4

In this step, the 2H-chromene compound of formula (LXI) is prepared from the 4-acyloxychroman of formula (LX) by elimination of an acid of formula $R^{11a}OH$ (in which R^{11a} is as defined above).

This elimination reaction can be carried out in the presence or absence of an acid-binding agent or catalyst. Examples of suitable such agents and catalysts include: inorganic acids, such as hydrochloric acid, sulphuric acid, nitric acid or phosphoric acid; organic carboxylic acids, such as acetic acid, tartaric acid or maleic acid; organic sulphonic acids, such as p-toluenesulphonic acid, naphthalenesulphonic acid or methanesulphonic acid; inorganic salts, such as ammonium chloride or calcium chloride; organic bases, such as pyridine or triethylamine; silica gel; and alumina. Of these, we prefer an organic carboxylic or sulphonic acid, such as acetic acid or p-toluenesulphonic acid.

It is not always necessary to employ a solvent for this elimination reaction and, where a solvent is employed, its nature is not critical, provided that it has no adverse effect on the reaction. Suitable solvents include, for example: alcohols, such as methanol, ethanol or isopropanol; ketones, such as acetone or methyl ethyl ketone; ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene or xylene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptane; halogenated hydrocarbons, such as methylene chloride or chloroform; organic acids, such as acetic acid or propionic acid; organic bases, such as pyridine or triethylamine; amides, such as dimethylformamide or dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; sulphones, such as sulpholane; and water. Of these, we prefer aromatic hydrocarbons (such as benzene) or organic acids (such as acetic acid).

Where an acid-binding agent or catalyst is employed, the relative proportions of such agent or catalyst and the compound of formula (LX) are not particularly critical. We generally prefer to employ the agent or catalyst and the compound of formula (LX) in a molar ratio of from 0.01:1 to 10:1, more preferably from 0.1:1 to 3:1.

The reaction will take place over a wide range of temperatures and the exact temperature chosen is not particularly critical. In general, we prefer to carry out the reaction at a temperature within the range from 0°C to 120°C, more preferably from 40°C to 100°C. The time required for the reaction may vary widely, depending upon many factors, notably the nature of the reagents and the reaction temperature; however, at a temperature within the preferred ranges indicated above, a period of from several minutes to several days, commonly from 10 minutes to 10 hours, will normally suffice.

Step F5

In this step, the chroman derivative of formula (XXXIV) is prepared by the reductive hydrogenation of the 2H-chromene derivative of formula (LXI).

Catalytic hydrogenation is preferably employed. Suitable catalysts include, for example, palladium-on-carbon, Raney nickel or platinum oxide, of which palladium-on-carbon is preferred. The partial pressure of hydrogen may vary widely, for example from 1 to 100 atmospheres (about 1 to 101 bars), more preferably from 1 to 6 atmospheres (about 1 to 6 bars). The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it does not interfere with the reaction. Suitable solvents include, for example: alcohols, such as methanol or ethanol; aromatic hydrocarbons, such as benzene or toluene; ethers, such as tetrahydrofuran; organic acids, such as acetic acid; water; or a mixture of any two or more thereof.

The reaction will take place over a wide range of temperatures and the exact temperature chosen is not particularly critical; however, we generally prefer to carry out the reaction at a temperature from room temperature to 50°C. The time required for the reaction may vary widely, depending upon many factors, notably the nature of the reagents

and the reaction temperature; however, at a temperature within the indicated range, a period of from several minutes to 20 hours will normally suffice.

The α-halocarboxylic acid derivative of formula (XXX) may then be prepared as described in step A4 from this compound of formula (XXXIV).

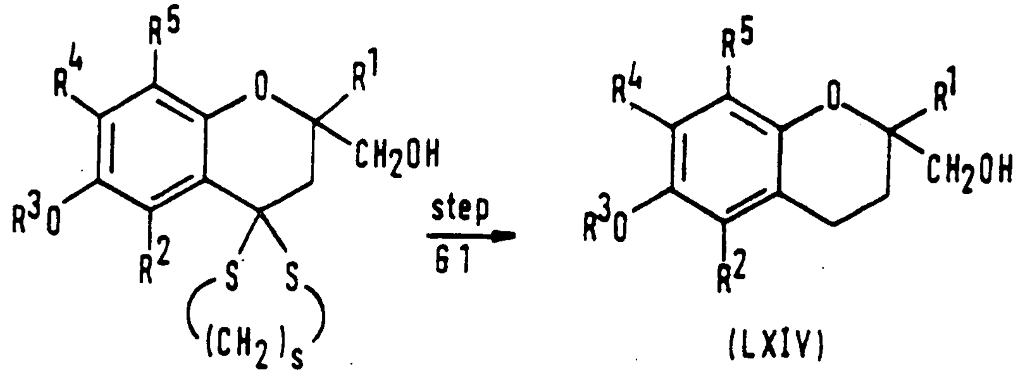
Steps F1, F3 (or F2 + F4), F5, A4 and the final step of reacting the α-halocarboxylic acid derivative (XXX) with thiourea to give the desired thiazolidine derivative of the invention can, if desired, be carried out in succession without intermediate isolation of the products of any of these steps.

Moreover, these steps are not necessarily carried out in the sequence described above and they may be carried out in any appropriate order. For example, one suitable alternative sequence would comprise: first, reducing the nitro group in the compound of formula (XLIX) by a step analogous to step F5 to give the corresponding amino compound; reducing the carbonyl group at the 4-position of the chroman ring by a step analogous to step F1 to give a 4-hydroxychroman compound; dehydrating this 4-hydroxychroman compound by a step analogous to step F3 (or acylating and then eliminating the acid by steps analogous to steps F2 and F4), to give a 2H-chromene compound; and finally hydrog nating the 2H-chromene compound by a step analogous to st p F5.

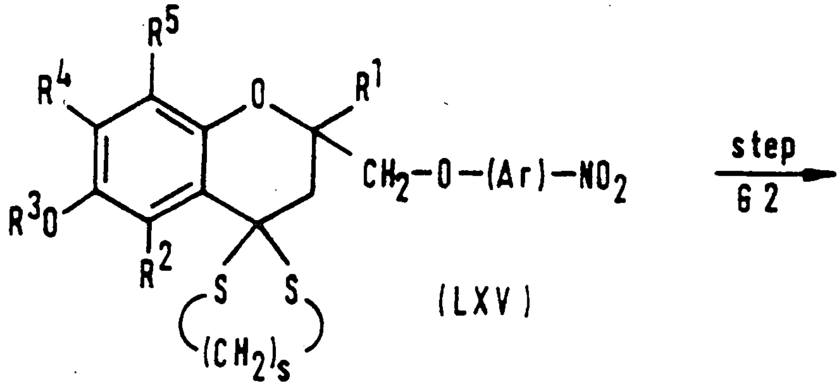
Method G

This process is useful for converting a chroman derivative, such as those prepared in steps E5 and E6 of Method E, having a carbonyl group as W at the 4-position to the corresponding compound where W is a methylene group. The compounds prepared as described in steps E5 and E6 are first, if necessary, deprotected, to remove the protecting group R^{20} at the 6-position. The resulting free hydroxy group is then acylated.

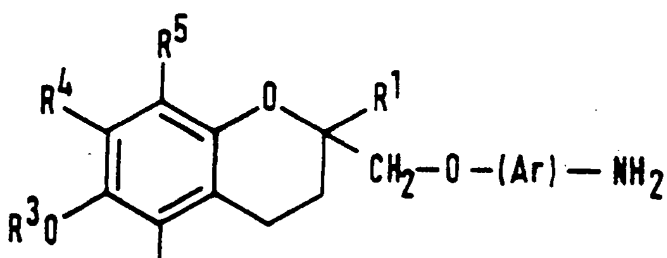
The resulting compound then has its carbonyl group protected, as described in step E2, to give a compound of formula (LXIII) or (LXV). These compounds are then hydrogenated, to give the corresponding compounds of formulae (LXIV) or (LXVI), as shown below:



(LXIII) (LXIV)



(LXV)



(LXVI)

In the above formulae, R¹-R⁵ and Ar are as defined above; s is 2, 3 or 4.

The hydrogenation is preferably effected in the presence of a catalyst, preferably a nickel catalyst, such as Raney nickel.

The hydrogen partial pressure may vary widely, for example from 1 to 100 atmospheres (about 1 to 101 bars), more preferably from 1 to 6 atmospheres (about 1 to 6 bars).

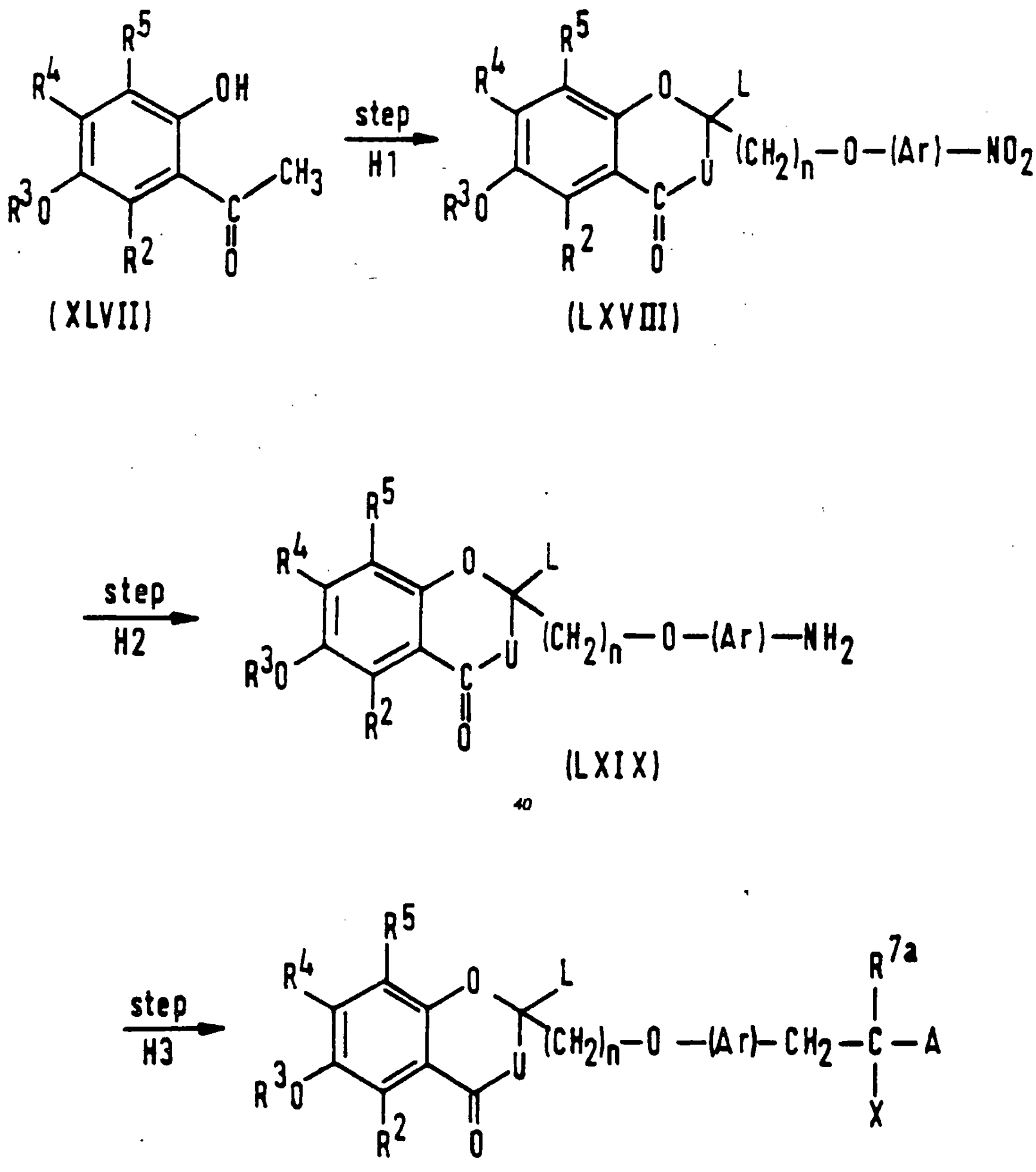
The reaction is pref rably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adv rse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol or ethanol; aromatic hydrocarbons, such as benzene or toluene; ethers, such as tetrahydrofuran; organic acids, such as acetic acid; water; and mixtures of any two or more thereof.

The reaction will take place over a wide range of temperatures, for example for room temperature to 50°C. The time required for the reaction will vary, depending upon many factors, notably the nature of the reagents and the reaction temperatur , but a period of from several minutes to 20 hours will normally suffice.

The resulting compounds of formulae (LXIV) and (LXVI) may thereaft r be treated by any of the appropriate processes described above to give the desired compounds of formula (II).

Method H

This method can be used to prepare compounds of formula (XIII), having a group L at the 2-position of the chroman ring and where W is a carbonyl group, as illustrated in the following reaction scheme:



(XLVII) (LXVIII) (LXIX) (XIII)

In the above formulae, R^2-R^6, U, L, n, Ar, R^{7a}, X and A are as defined above.

Preferably, L represents a group of formula -OR^3 and U represents a methylene group. However, if desired, L, the carbon atom to which it is attached and U may together represent a double bond.

Step H1

In this step, the compound of formula (XLVII) is reacted with a compound of formula (LXX):

O_2N-(Ar)-O-$(CH_2)_n$-COX (LXX)

(in which Ar, n and X are as defined above), followed by treatment with an organic base, such as sodium ethoxide or potassium t-butoxide. The reaction is otherwise similar to that of step C2 of Method C and may be carried out under the same reaction conditions.

Step H2

This is equivalent to step A3 and may be carried out using the same reagents and under the same reaction conditions.

Step H3

This is equivalent to step A4 of Method A and may be carried out using the same reagents under the same reaction conditions.

Of Methods A-H, Methods A, B, C, D, E, F and H are preferred, Methods A, C, D, E, F and H being more preferred and a combination of Methods D, F and A being most preferred. A particularly preferred combination of reactions comprises steps F1, F3 (or F2 plus F4), F5, A4 and finally reaction with thiourea to give a compound of formula (I) in which R^7 is R^{7a} and R^4 is a hydrogen atom. In particular, we prefer this sequence of steps where Ar represents a p-phenylene group.

In the compounds of formula (II), the carbon atom at the 2-position of the chroman ring and the carbon atom to which the substituents X, A and R^{7a} are attached are both asymmetric and accordingly a number of isomers are possible. The present invention envisages both the individual isolated isomers as well as mixtures thereof. Individual isomers may be prepared by stereospecific synthesis techniques or by separation of mixtures of isomers. Alternatively, the mixtures of isomers may be employed as such.

We have found that the α-halocarboxylic acid derivatives of formula (II) have the ability to lower the levels of blood lipid peroxides, blood triglycerides and blood cholesterol, indicating that, in addition to their use as intermediates in the preparation of the compounds of the invention, they may also have in themselves therapeutic value in the treatment of hyperlipemia.

The compounds of formula (II) prepared as described above can, if desired, be converted to various of their hydrolysis products or may be transesterified or converted to salts, for example such metal salts as the sodium, potassium, calcium or aluminium salts. Alternatively, they can be converted from metal salts or from compounds having free hydroxyphenyl groups or free carboxy groups to derivatives thereof, for example as follows:

Compounds in which R^3 represents a hydrogen atom and A represents a carboxy group can be prepared by hydrolysis of the corresponding compound of formula (II) in which, for example, R^3 represents an acyl group and A represents an alkoxycarbonyl group. This reaction is preferably effected in the presence of a base, for example: an inorganic base, such as an alkali metal carbonate - (e.g. sodium carbonate or potassium carbonate) or an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide); or an organic base, such as an alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide or potassium t-butoxide). The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: lower alcohols, such as methanol or ethanol; ethers, such as tetrahydrofuran or dioxane; water; or mixtures of any two or more thereof.

The molar ratio of the compound of formula - (II) to the base is preferably from 1:1 to 1:5, more preferably from 1:2 to 1:3. Although the reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, particularly the natures of the starting material, base and solvent employed, the reaction is generally carried out at a temperature of from -10°C to +30°C, more preferably from 0 to 10°C, and the reaction time is generally from several minutes to several tens of hours.

The compound of formula (II) in which R^3 represents a hydrogen atom and A represents an alkoxycarbonyl group can be prepared by solvolysis of the corresponding compound in which R^3 represents an acyl group and A represents an alkoxycarbonyl group. This is carried out in the presence of a base, preferably an alkali metal alkoxide, such as sodium methoxide, sodium ethoxide or potassium t-butoxide. The reaction is preferably effected in th presence of a solvent, for xample: an alcohol, such as methanol, ethanol, propanol, isopropanol or t-butanol; an ether; such as tetrahydrofuran or dioxane; or a mixture of any two or more thereof. If the alkoxycarbonyl group

represented by A in the starting material is to be k pt intact, it is preferred that the alkali metal alkoxide should be the alkoxide corresponding to this alkoxycarbonyl group and that the solvent should be an alcohol, which likewise corresponds to the alkoxycarbonyl group. However, the alkoxycarbonyl group in the starting material may, if desired, be converted into any other alkoxycarbonyl group by suitable choice of the alkali metal alkoxide and the alcohol solvent.

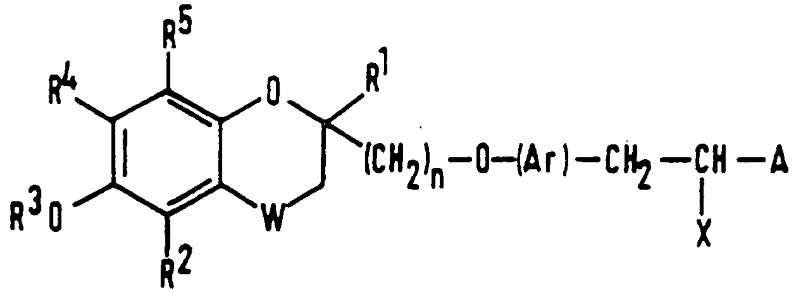
The molar ratio of the compound of formula (II) to the base is preferably from 1:1 to 1:3, more preferably from 1:1 to 1:2. The reaction conditions, especially the reaction temperature and reaction time, may vary, depending upon a number of factors, particularly the natures of the starting materials, bases and solvents employed, but the reaction is preferably carried out at a temperature of from -10°C to +30°C, more preferably from 0 to 10°C, for a period of from several minutes to several tens of hours.

Compounds of formula (II) in which R^3 represents an acyl group and A represents a carboxy group may be prepared by hydrolysis of the corresponding compound of formula (II) in which R^3 represents an acyl group and A represents an alkoxycarbonyl group. In this case, the hydrolysis is effected in the presence of an inorganic base (for example an alkali metal carbonate, such as sodium carbonat or potassium carbonate, or an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide) or in the presence of another base such as an alkali metal alkoxide (for example sodium methoxide, sodium ethoxide or potassium t-butoxide). This reaction is preferably effected in the presence of a solvent, for example: a lower alcohol, such as methanol or ethanol; an ether, such as tetrahydrofuran or dioxane; water; or a mixture of any two or more thereof. The molar ratio of the compound of formula (II) to the base is preferably from 1:1 to 1:5, more preferably from 1:1 to 1:2. The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, especially the natures of the starting materials, bases and solvents employed, but the reaction is normally effected at a temperature of from -10°C to +30°C, more preferably from 0 to 10°C for a period of from several minutes to several tens of hours.

Of the compounds of formula (II) which exhibit the therapeutic effects mentioned above and which also form part of the present invention, preferred compounds are those listed below in Table 27.

In this Table, the abbreviations used are as previously defined in relation to Tables 1-26.

Compounds of formula (II-27):



(II-27)

are as defined in Table 27:

Table 27

Table 27. (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	n	Ar	X	A
1001	Me	Me	H	Me	Me	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1002	Me	Me	Ac	Me	Me	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1003	Me	Me	H	Me	Me	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1004	Me	Me	Ac	Me	Me	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1005	Me	Me	H	Me	Me	$>CH_2$	1	2,5-Pydi	Cl	-COOEt
1006	Me	Me	Ac	Me	Me	$>CH_2$	1	2,5-Pydi	Cl	-COOEt
1007	Me	Me	H	Me	Me	>C=O	1	2,5-Pydi	Cl	-COOEt
1008	Me	Me	Ac	Me	Me	>C=O	1	2,5-Pydi	Cl	-COOEt
1009	Me	H	H	_t_-Bu	H	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1010	Me	H	Ac	_t_-Bu	H	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1011	Me	H	H	_t_-Bu	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1012	Me	H	Ac	_t_-Bu	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1013	Me	H	H	_t_-Bu	H	$>CH_2$	1	2,5-Pydi	Cl	-COOEt
1014	Me	H	Ac	_t_-Bu	H	$>CH_2$	1	2,5-Pydi	Cl	-COOEt
1015	Me	H	H	_t_-Bu	H	>C=O	1	2,5-Pydi	Cl	-COOEt

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	n	Ar	X	A
1016	Me	H	Ac	t-Bu	H	>C=O	1	2,5-Pydi	Cl	-COOEt
1017	Me	H	Ac	TMB	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1018	Me	H	Ac	TMB	H	>C=O	1	p-Phn	Cl	-COOEt
1019	Me	H	Ac	TMB	H	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1020	Me	H	Ac	TMB	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1021	Me	H	Ac	TMB	H	$>CH_2$	1	2,5-Pydi	Cl	-COOEt
1022	Me	H	Ac	TMB	H	$>CH_2$	2	p-Phn	Cl	-COOMe
1023	Et	Me	Boz	Me	Me	>C=O	1	5-Me-1,3-Phn	Cl	-COOH
1024	iBu	Me	4-MeBoz	Me	H	>C=O	1	2,5-Pydi	Cl	$-COOHN_4$
1025	nPn	Me	Ac	Me	Me	$>CH_2$	1	2,5-Pydi	Cl	-COOMe
1026	Hx	Me	Ac	Me	Me	$>CH_2$	1	p-Phn	Cl	-COOEt

Table 27 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	n	Ar	X	A
1027	*i*Hx	Me	Ac	Me	Me	>C=O	1	p-Phn	Cl	-COOMe
1028	Hx	Me	Ac	Me	Me	>CH_2	1	6-Me-1,3-Phn	Cl	-COOH
1029	Hp	H	H	*t*Bu	H	>CH_2	1	2,5-Pydi	Cl	-COOEt
1030	Oc	Me	Ac	Me	Me	>CH_2	1	p-Phn	Cl	-COOEt
1031	Oc	Me	Ac	Me	Me	>C=O	1	p-Phn	Cl	-COOEt
1032	Oc	Me	Ac	Me	Me	>CH_2	1	6-Me-1,3-Phn	Cl	-COOEt
1033	Oc	Me	Ac	Me	Me	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1034	Oc	Me	Ac	Me	Me	>CH_2	1	2,5-Pydi	Cl	-COOEt
1035	Oc	Me	Ac	Me	Me	>C=O	1	2,5-Pydi	Cl	-COOEt
1036	Oc	H	Ac	*t*-Bu	H	>CH_2	1	p-Phn	Cl	-COOEt
1037	Oc	H	Ac	*t*-Bu	H	>C=O	1	p-Phn	Cl	-COOEt
1038	Oc	H	Ac	*t*-Bu	H	>CH_2	1	6-Me-1,3-Phn	Cl	-COOEt
1039	Oc	H	Ac	*t*-Bu	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1040	Oc	H	Ac	*t*-Bu	H	>CH_2	1	2,5-Pydi	Cl	-COOEt
1041	Oc	H	Ac	*t*-Bu	H	>C=O	1	2,5-Pydi	Cl	-COOEt

Table 27 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	n	Ar	X	A
1042	Oc	H	Ac	TMB	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1043	Oc	H	Ac	TMB	H	>C=O	1	p-Phn	Cl	-COOEt
1044	Oc	H	Ac	TMB	H	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1045	Oc	H	Ac	TMB	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1046	Oc	H	Ac	TMB	H	$>CH_2$	1	2,5-Pydi	Cl	-COOEt
1047	Oc	H	Ac	TMB	H	>C=O	1	2,5-Pydi	Cl	-COOEt
1048	5,5-DMH	Me	Ac	Me	Me	$>CH_2$	1	p-Phn	Cl	-COOEt
1049	Bz	iPr	H	iPr	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1050	Nn	Me	H	Me	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1051	Dc	Me	Ac	MeO	MeO	$>CH_2$	1	p-Phn	Cl	-COOEt
1052	3,7-DMO	Me	H	Me	Me	$>CH_2$	1	p-Phn	Cl	-COOEt
1053	3,7-DMO	Me	Ac	Me	Me	$>CH_2$	1	p-Phn	Cl	-COOEt
1054	3,7-DMO	Me	Ac	Me	Me	>C=O	1	p-Phn	Cl	-COOEt

Table 27 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	n	Ar	X	A
1055	3,7-DMO	Me	Ac	Me	Me	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1056	3,7-DMO	Me	Ac	Me	Me	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1057	3,7-DMO	Me	Ac	Me	Me	$>CH_2$	1	2,5-Pydi	Cl	-COOEt
1058	3,7-DMO	Me	Ac	Me	Me	>C=O	1	2,5-Pydi	Cl	-COOEt
1059	3,7-DMO	H	H	tBu	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1060	3,7-DMO	H	Ac	tBu	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1061	3,7-DMO	H	H	tBu	H	>C=O	1	p-Phn	Cl	-COOEt
1062	3,7-DMO	H	Ac	tBu	H	>C=O	1	p-Phn	Cl	-COOEt
1063	3,7-DMO	H	H	tBu	H	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1064	3,7-DMO	H	Ac	tBu	H	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1065	3,7-DMO	H	H	tBu	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1066	3,7-DMO	H	Ac	tBu	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1067	3,7-DMO	H	Ac	tBu	H	$>CH_2$	1	2,5-Pydi	Cl	-COOEt

Table 27 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	n	Ar	X	A
1068	3,7-DMO	H	Ac	tBu	H	>C=O	1	2,5-Pydi	Cl	-COOEt
1069	3,7-DMO	H	Ac	TMB	H	>CH_2	1	p-Phn	Cl	-COOEt
1070	3,7-DMO	H	Ac	TMB	H	>C=O	1	p-Phn	Cl	-COOEt
1071	3,7-DMO	H	Ac	TMB	H	>CH_2	1	6-Me-1,3-Phn	Cl	-COOEt
1072	3,7-DMO	H	Ac	TMB	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1073	3,7-DMO	H	AC	TMB	H	>CH_2	1	2,5-Pydi	Cl	-COOEt
1074	3,7-DMO	H	Ac	TMB	H	>C=O	1	2,5-Pydi	Cl	-COOEt
1075	3,7-DMO	H	Boz	TMB	H	>CH_2	1	p-Phn	Cl	-COOEt
1076	3,7-DMO	H	Ac	Me	H	>CH_2	1	p-Phn	Cl	-COOH
1077	7,7-DMO	Me	H	Me	Me	>CH_2	1	p-Phn	Cl	-COOEt
1078	7,7-DMO	Me	Ac	Me	Me	>CH_2	1	p-Phn	Cl	-COOEt
1079	7,7-DMO	Me	H	Me	Me	>C=O	1	p-Phn	Cl	-COOEt
1080	7,7-DMO	Me	Ac	Me	Me	>C=O	1	p-Phn	Cl	-COOEt

Table 27 (cont)

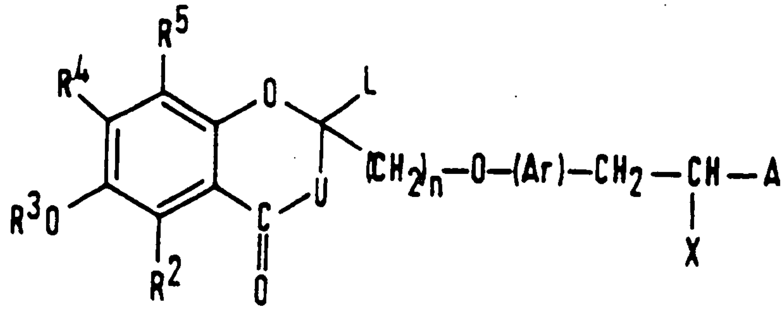
Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	n	Ar	X	A
1081	7,7-DMO	Me	Ac	Me	Me	$>CH_2$	1	6-Me-1,3-Phn	Cl	-COOEt
1082	7,7-DMO	Me	Ac	Me	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOEt
1083	7,7-DMO	Me	Ac	Me	H	$>CH_2$	1	2,5-Pydi	Cl	-COOEt
1084	7,7-DMO	Me	Ac	Me	H	>C=O	1	2,5-Pydi	Cl	-COOEt
1085	7,7-DMO	H	Ac	<u>t</u>Bu	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1086	7,7-DMO	H	Ac	<u>t</u>Bu	H	>C=O	1	p-Phn	Cl	-COOEt
1087	7,7-DMO	H	Ac	TMB	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1088	Bz	Me	H	Me	Me	$>CH_2$	1	p-Phn	Cl	-COOEt

Table 27 (cont)

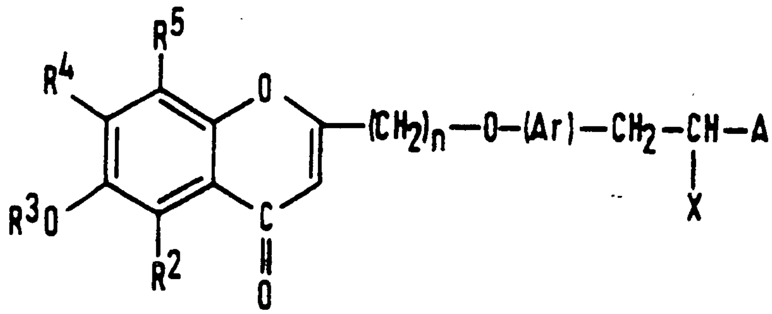
Cpd. No.	R^1	R^2	R^3	R^4	R^5	W	n	Ar	X	A
1089	Bz	Me	Ac	Me	Me	$>CH_2$	1	p-Phn	Cl	-COOEt
1090	Bz	Me	H	Me	Me	>C=O	1	p-Phn	Cl	-COOEt
1091	Bz	Me	Ac	Me	Me	>C=O	1	p-Phn	Cl	-COOEt
1092	Bz	H	H	tBu	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1093	Bz	H	H	TMB	H	$>CH_2$	1	p-Phn	Cl	-COOEt
1094	Me	Me	$HOOCCH_2$-	Me	Me	$>CH_2$	1	p-Phn	Cl	-COOEt
1095	Me	Me	$EtOOCCH_2$-	Me	Me	>C=O	1	p-Phn	Cl	-COOEt
1096	Me	H	$HOOCCH_2$-	tBu	H	$>CH_2$	1	2,5-Pydi	Cl	-COOH
1097	3,7-DMO	H	$HOOC(CH_2)_2$-	tBu	H	$>CH_2$	2	p-Phn	Br	-COOH
1098	Me	H	$HOOCCMe_2$-	TMB	H	>C=O	1	6-Me-1,3-Phn	Cl	-COOPr

In addition, other compounds useful as intermediates are shown in Tables 28 and 29, the abbreviations used again being as defined in relation to Tables 1-26.

Compounds of formulae (XIII-28) and (XIII-29):



(XIII-28)



(XIII-29)

are as defined in Table 27 and 28, respectively:

Table 28

Table 28 (cont)

Cpd. No.	L	U	R^2	R^3	R^4	R^5	n	Ar	X	A
2001	-OH	$>CH_2$	Me	H	Me	Me	1	p-Phn	Cl	-COOH
2002	-OH	$>CH_2$	Me	Ac	Me	Me	1	p-Phn	Cl	-COOEt
2003	-OH	$>CH_2$	Me	H	Me	Me	2	p-Phn	Cl	-COOH
2004	-OH	$>CH_2$	Me	H	Me	Me	1	6-Me-1,3-Phn	Cl	-COOMe
2005	-OH	$>CH_2$	Me	Ac	Me	Me	1	6-Me-1,3-Phn	Cl	-COOEt
2006	-OH	$>CH_2$	Me	H	Me	Me	1	2,5-Pydi	Cl	-COOH
2007	-OH	$>CH_2$	Me	Ac	Me	Me	1	2,5-Pydi	Cl	-COOiPr
2008	-OH	$>CH_2$	H	H	tBu	H	1	p-Phn	Cl	-COOH
2009	-OH	$>CH_2$	H	Ac	tBu	H	1	p-Phn	Cl	-COOEt
2010	-OH	$>CH_2$	H	H	tBu	H	1	6-Me-1,3-Phn	Cl	-COOH
2011	-OAc	$>CH_2$	H	Ac	tBu	H	1	6-Me-1,3-Phn	Cl	-COO-tBu
2012	-OH	$>CH_2$	H	H	tBu	H	1	2,5-Pydi	Cl	-COOH
2013	-OH	$>CH_2$	H	Ac	tBu	H	1	2,5-Pydi	Cl	-COOPh

Table 29

Cpd. No.	L	U	R^2	R^3	R^4	R^5	n	Ar	X	A
2014	-OH	$>CH_2$	H	H	TMB	H	1	p-Phn	Cl	-COOH
2015	-OH	$>CH_2$	H	H	TMB	H	1	6-Me-1,3-Phn	Cl	-COOH
2016	-OH	$>CH_2$	H	H	TMB	H	1	2,5-Pydi	Cl	-COOH

Table 29 (cont)

Cpd. No.	R^2	R^3	R^4	R^5	n	Ar	X	A
2017	Me	H	Me	Me	1	p-Phn	Cl	-COOH
2018	Me	Ac	Me	Me	1	p-Phn	Cl	-COOEt
2019	Me	H	Me	Me	1	6-Me-1,3-Phn	Cl	-COOH
2020	Me	Ac	Me	Me	1	6-Me-1,3-Phn	Cl	-COOMe
2021	Me	H	Me	Me	1	2,5-Pydi	Cl	-COOH
2022	Me	Ac	Me	Me	1	2,5-Pydi	Cl	-COOEt
2023	H	H	tBu	H	1	p-Phn	Cl	-COOH
2024	H	H	tBu	H	1	6-Me-1,3-Phn	Cl	-COOH
2025	H	H	tBu	H	1	2,5-Pydi	Cl	-COOH
2026	H	H	TMB	H	1	p-Phn	Cl	-COOH
2027	H	H	TMB	H	1	p-Phn	Cl	-COOiBu

Cpd. No.	R^2	R^3	R^4	R^5	n	Ar	X	A
2028	Me	$HOOC-CH_2-$	Me	Me	1	p-Phn	Cl	-COOH
2029	Me	$EtOOC-CH_2-$	Me	Me	1	p-Phn	Cl	-COOEt
2030	Me	$EtOOC-CH_2-$	Me	Me	1	2,5-Pydi	Cl	-COOEt
2031	H	$HOOC-CH_2-$	tBu	H	1	p-Phn	Cl	-COOH
2032	H	$EtOOC-CH_2-$	tBu	H	1	6-Me-1,3-Phn	Cl	-COOEt
2033	H	$HOOC-CH_2-$	TMB	H	1	p-Phn	Cl	-COOH
2034	H	$BuOOC-CH_2-$	TMB	H	1	p-Phn	Cl	COOBu
2035	H	$HOOC-CH_2-$	TMB	H	1	p-Phn	Br	-COOH
2036	Me	$HOOCCMe_2-$	Me	Me	1	p-Phn	Cl	-COOH
2037	H	$HOOCCMe_2-$	tBu	H	1	p-Phn	Cl	-COOH
2038	H	$HOOCCMe_2-$	TMB	H	1	p-Phn	Cl	-COOH
2039	H	$EtOOCCMe_2-$	Me	H	1	p-Phn	Cl	-COOEt

The compounds of the invention have shown a very strong ability to inhibit the oxidation of unsaturated fatty acids and their esters (such as linolic acid and ethyl linolate) and, accordingly, it is expected that these compounds will be able to prevent the oxidation of phospholipids containing a high content of unsaturated fatty acids from oxidation, even *in vivo*.

The compounds of the invention have been shown to have a very strong ability to lower the level of lipid peroxides, as demonstrated, *inter alia*, by the test against rat liver microsomal lipid peroxidation described in Biochem. Biophys. Res. Commun., 95, 734 (1980). In addition, in experiments using alloxan-induced hyperlipaemic mice, the compounds have demonstrated the ability to lower blood lipid peroxide, triglyceride and cholesterol levels. The compounds have also shown the ability to lower blood sugar levels in a test using genetically diabetic mice of the KK strain. Moreover, the compounds of the invention are less toxic than many known compounds to experimental animals such as rats or mice and result in little anorexia, inhibition of body weight increase and liver hypertrophy.

The compounds of the invention have also shown the ability to inhibit the activity of aldose reductase.

Accordingly, it is considered that the compounds of the present invention will be useful for the therapeutic treatment of human hyperlipaemia, diabetes and complications thereof, especially diabetes mellitus. The compounds of the invention may be administered orally, for example in the form of tablets, capsules, powders or granules, or parenterally, for example by injection or in the form

of a suppository. The recommended dosage will, of course, vary depending upon the age and body weight of th patient as well as the nature and severity of the disease. However, for an adult human patient, a daily dose of from 50 mg to 5 g - (which may be administered in a single dose or in divided doses) is recommended in the treatment of hyperlipaemia, diabetes mellitus and complications thereof.

The following Examples illustrate the preparation of various of the compounds of the present invention. Preparation of various of the starting materials employed in the Examples is illustrated in the subsequent Preparations. The subsequent Test Examples illustrate the valuable biological properties of these compounds.

In the nuclear magnetic resonance spectra reported in the Examples and Preparations, the abbreviation "nd" means that precise identification of the signal was not possible because of overlap by other signals or the absorption of the solvent.

EXAMPLE 1

5-[4-(6-Hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (Step D4)

A mixture of 0.5 g of ethyl 3-[4-(6-acetoxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 9), 0.2 g of thiourea and 0.8 g of sulpholane was heated at 120-135°C for 4 hours under a nitrogen stream. A mixture of 1 ml of concentrated hydrochloric acid, 1 ml of water and 5 ml of ethylene glycol monomethyl ether was then added to the reaction mixture, and the mixture was heated under reflux for 6 hours. The reaction mixture was then poured into water and extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by preparative silica gel thin layer chromatography using a 1:1 by volume mixture of hexane and ethyl acetate as developing solvent, to give the title compound, softening at 70-78°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.97 (6H, doublet, J=6Hz);

1.5-2.1 (3H, nd);

2.12 (3H, singlet);

2.21 (3H, singlet);

2.53 (3H, singlet);

2.77 & 2.99 (2H, AB type, J=16Hz);

2.8-3.2 (1H, nd);

3.41 (1H, doublet of doublets, J=4 & 14Hz);

4.06 (2H, AB type, J=10Hz);

4.43 (1H, doublet of doublets, J=4 & 9Hz);

4.6-5.3 (1H, broad singlet, disappeared on adding heavy water);

6.81 (2H, doublet, J=9Hz);

7.12 (2H, doublet, J=9Hz);

8.7-9.3 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 2

5-[4-(6-Acetoxy-5,7,8-trimethyl-2-octylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

A mixture of 2.1 g of ethyl 3-[4-(6-acetoxy-5,7,8-trimethyl-2-octylchroman-2-ylmethoxy)-phenyl]-2-chloropropionate (prepared as described in Preparation 18), 0.35 g of thiourea and 2.5 ml of sulpholane was heated for 7 hours at 120-130°C under a nitrogen atmosphere. The reaction mixture was then dissolved in benzene. The benzene solution was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography, eluted with a 10:1 by volume mixture of benzene and ethyl acetate, to give the title compound as a slightly yellow, foamy solid.

Rf value on silica gel thin layer chromatography = 0.55 (developing solvent, benzene:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.7-1.0 (3H, multiplet);

1.1-2.0 (16H, multiplet);

1.97 (3H, singlet);

2.03 (3H, singlet);

2.08 (3H, singlet);

2.31 (3H, singlet);

2.60 (2H, broad triplet, J=6Hz);

3.03 (1H, doublet of doublets, J=10 & 15Hz);

3.44 (1H, doublet of doublets, J=3 & 15Hz);

3.92 (2H, singlet);

4.45 (1H, doublet of doublets, J=3 & 10Hz);

6.85 (2H, doublet, J=9Hz);

7.13 (2H, doublet, J=9Hz);

8.0-8.9 (1H, broad, disappeared on adding heavy water).

EXAMPLE 3

5-[4-(6-Hydroxy-5,7,8-trimethyl-2-octylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

A mixture of 2.1 g of ethyl 3-[4-(6-acetoxy-5,7,8-trimethyl-2-octylchroman-2-ylmethoxy)-phenyl]-2-chloropropionate (prepared as described in Preparation 18), 0.35 g of thiourea and 2.5 ml of sulpholane was heated for 7 hours at 120-130°C under a nitrogen atmosphere. A mixture of 3.6 ml of 2N aqueous hydrochloric acid and 5 ml of ethylene glycol monomethyl ether was then added to the reaction mixture, after which it was heated for a further 5 hours at 85-90°C. The reaction mixture was then poured into water and extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography, using a 10:1 by volume mixture of benzene and ethyl acetate as eluent, to give the title compound as a slightly yellow, foamy solid.

Rf value on silica gel thin layer chromatography = 0.43 (tailing) (developing solvent, benzene:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.7-1.0 (3H, multiplet);

1.1-2.1 (16H, multiplet);

2.10 (6H, singlet);

2.15 (3H, singlet);

2.61 (2H, broad triplet, J=6Hz);

3.05 (1H, doublet of doublets, J=10 & 15Hz);

3.42 (1H, doublet of doublets, J=3 & 15Hz);

3.92 (2H, singlet);

4.22 (1H, singlet, disappeared on adding heavy water);

4.47 (1H, doublet of doublets J=3 & 10Hz);

6.85 (2H, doublet, J=9HZ);

7.13 (2H, doublet, J=9Hz);

8.33 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 4

5-[4-(6-Acetoxy-2-methyl-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione

The procedure described in Example 2 was repeated, but using 7.0 g of ethyl 3-{4-[6-acetoxy-2-methyl-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]phenyl}-2-chloropropionate (prepared as described in Preparation 23), 1.2 g of thiourea and 9 ml of sulpholane, to give the title compound as a slightly yellow glassy solid, softening at 75-80°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.79 (9H, singlet;

1.36 (6H, singlet);

1.45 (3H, singlet);

1.66-2.28 (2H, nd);

1.80 (2H, singlet);

2.29 (3H, singlet);

2.73 (2H, broad triplet, J=6Hz);

3.28 (1H, doublet of doublets, J=9 & 14Hz);

3.45 (1H, doublet of doublets, J=4 & 14Hz);

3.93 (2H, AB type, J = 9Hz);

4.49 (1H, doublet of doublets, J = 4 & 9Hz);

6.75 (1H, singlet);

6.86 (1H, singlet);

6.90 (2H, doublet, J = 9Hz);

7.13 (2H, doublet, J = 9Hz);

8.1-8.7 (1H, broad, disappeared on adding heavy water).

EXAMPLE 5

5-{4-[6-Hydroxy-2-methyl-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy}-benzyl}thiazolidine-2,4-dione

The procedure described in Example 3 was repeated, but using 7.0 g of ethyl 3-{4-[6-acetoxy-2-methyl-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]phenyl}-2-chloropropionate (prepared as described in Preparation 23), 1.2 g of thiourea, 9 ml of sulpholane, 13 ml of 2N hydrochloric acid and 20 ml of ethylene glycol monomethyl ether, to give the title compound as a slightly yellow glassy solid, softening at 80-85°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.78 (9H, singlet);

1.41 (9H, singlet);

1.60-2.30 (2H, nd);

1.91 (2H, singlet);

2.67 (2H, broad triplet, J = 6.5Hz);

3.07 (1H, doublet of doublets, J = 10 & 14Hz);

3.45 (1H, doublet of doublets, J = 4 and 14Hz);

3.93 (2H, AB type, J = 9Hz);

4.45 (1H, singlet, disappeared on adding heavy water);

4.49 (1H, doublet of doublets, J = 4 & 10Hz);

6.34 (1H, singlet);

6.77 (1H, singlet);

6.88 (2H, doublet, J = 9Hz);

7.17 (2H, doublet, J = 9Hz);

8.4 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 6

5-{4-[6-Acetoxy-2-methyl-4-oxo-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy}-benzyl}thiazolidine-2,4-dione

The procedure described in Example 2 was repeated, but using 7.3 g of ethyl 3-{4-[6-acetoxy-2-methyl-4-oxo-7-(1,1,3,3-tetramethylbutyl)-chroman-2-ylmethoxy]phenyl}-2-chloroproprionate (prepared as described in Preparation 25), 1.3 g of thiourea and 8 ml of sulpholane, to give the title compound as a slightly yellow powder, softening at 80-88°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.78 (9H, singlet);

1.37 (6H, singlet);

1.53 (3H, singlet);

1.83 (2H, singlet);

2.30 (3H, singlet);

2.70 (1H, doublet, J = 17Hz);

2.8-3.2 (1H, nd);

3.10 (1H, doublet, J = 17Hz);

3.45 (1H, doublet of doublets, J = 4 & 15Hz);

4.00 & 4.12 (2H, AB type, J = 9Hz);

4.48 (1H, doublet of doublets, J = 4 & 9Hz);

6.85 (2H, doublet, J = 9Hz);

7.02 (1H, singlet);

7.17 (2H, doublet, J = 9Hz);

7.51 (1H, singlet);

8.3-9.0 (1H, broad, disappeared on adding heavy water).

EXAMPLE 7

5-{4-[6-Hydroxy-2-methyl-4-oxo-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

A mixture of 5.2 g of 5-{4-[6-acetoxy-2-methyl-4-oxo-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]benzyl}-2-iminothiazolidin-4-one (prepared as described in Preparation 26), 16 ml of 2N hydrochloric acid and 25 ml of ethylene glycol monomethyl ether was heated for 6 hours at 85-90°C under a nitrogen atmosphere. The reaction mixture was then poured into water and extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography, eluted with a 4:1 by volume mixture of benzene and ethyl acetate, to give the title compound as a slightly yellow foamy solid, softening at 100-105°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.77 (9H, singlet);

1.43 (6H, singlet);

1.52 (3H, singlet);

2.00 (2H, singlet);

2.70 (1H, doublet, J = 17Hz);

2.8-3.2 (1H, nd);

3.12 (1H, doublet, J = 17Hz);

3.43 (1H, doublet of doublets, J = 4 & 15Hz);

4.00 & 4.10 (2H, AB type, J = 9Hz);

4.49 (1H, doublet of doublets, J = 4 & 9Hz);

6.1 (1H, broad singlet, disappeared on adding heavy water);

6.85 (2H, doublet, J = 9Hz);

6.93 (1H, singlet);

7.15 (2H, doublet, J = 9Hz);

7.30 (1H, singlet);

8.2-9.3 (1H, broad, disappeared on adding heavy water).

EXAMPLE 8

5-{4-[2-(3,7-Dimethyloctyl)-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

The procedure described in Example 3 was repeated, but using 1.1 g of ethyl 3-{4-[6-acetoxy-2-(3,7-dimethyloctyl)-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy]phenyl}-2-chloropropionate (prepared as described in Preparation 33), 0.2 g of thiourea, 1.5 ml of sulpholane, 5 ml of 2N aqueous hydrochloric acid and 10 ml of ethylene glycol monomethyl ether, to give the title compound, as a slightly yellow powder, softening at 41-45°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.85 (9H, doublet, J = 7Hz);

1.0-2.0 (12H, multiplet);

2.13 (3H, singlet);

2.22 (3H, singlet);

2.55 (3H, singlet);

2.65-3.2 (3H, multiplet);

3.43 (1H, doublet of doublets, J = 4 & 14Hz);

4.05 (2H, singlet);

4.35-5.3 (1H, broad, disappeared on adding heavy water);

4.46 (1H, doublet of doublets, J = 4 & 10Hz);

6.83 (2H, doublet, J = 9Hz);

7.15 (2H, doublet, J = 9Hz);

8.0-9.5 (1H, broad, disappeared on adding heavy water).

EXAMPLE 9

5-[2-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)pyridin-5-ylmethyl]thiazolidine-2,4-dione

The procedure described in Example 3 was repeated, but using 3.8 g of ethyl 3-[2-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)pyridin-5-yl]-2-chloropropionate (prepared as described in Preparation 38), 0.77 g of thiourea, 5.0 ml of sulpholane, 4.5 ml of ethylene glycol monomethyl ether, 1.5 ml of concentrated hydrochloric acid and 4.5 ml of water, to give the title compound, softening at 87-94°C.

Nuclear Magnetic Resonance Spectrum (CDCl$_3$) δ ppm:

1.38 (3H, singlet);

1.7-2.3 (2H, multiplet);

2.06 (3H, singlet);

2.09 (3H, singlet);

2.14 (3H, singlet);

2.63 (2H, broad triplet, J=6Hz);

3.10 (1H, doublet of doublets, J=15 & 7.5Hz);

3.33 (1H, doublet of doublets, J=15 & 4.5Hz);

4.0-5.0 (1H, broad, disappeared on adding heavy water);

4.32 (3H, singlet);

4.47 (1H, doublet of doublets, J=7.5 & 4.5Hz);

6.75 (1H, doublet, J=9Hz);

7.46 (1H, doublet of doublets, J=9 & 3Hz);

8.02 (1H, doublet, J=3Hz).

EXAMPLE 10

5-[3-(7-t-Butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)-4-methylbenzyl]thiazolidine-2,4-dione

The procedure described in Example 3 was repeated, but using 2.4 g of ethyl 3-[3-(6-acetoxy-7-t-butyl-2-methyl-4-oxochroman-2-ylmethoxy)-4-methylphenyl]-2-chloropropionate (prepared as described in Preparation 42), 0.7 g of thiourea, 5 ml of sulpholane, 10 ml of 2N aqueous hydrochloric acid and 15 ml of ethylene glycol monomethyl eth r, to give the titl compound.

Rf value on silica gel thin layer chromatography = 0.44 (developing solvent, benzene:ethyl acetate = 1:1 by volum).

Nuclear Magnetic Resonance Spectrum (CDCl$_3$) δ ppm:

1.40 (9H, singlet);

1.57 (3H, singlet);

2.14 (3H, singlet);

2.77 (1H, doublet, J=16Hz);

3.01 (1H, doublet of doublets, J=10 & 14Hz);

3.07 (1H, doublet, J=16Hz);

3.44 (1H, doublet of doublets, J=4 & 14Hz);

3.99 & 4.13 (2H, AB type, J=10Hz);

4.50 (1H, doublet of doublets, J=4 & 10Hz);

5.84 (1H, broad singlet, disappeared on adding heavy water);

6.6-6.85 (2H, nd);

6.91 (1H, singlet);

7.08 (1H, doublet, J=7.5Hz);

7.31 (1H, singlet);

8.3-9.0 (1H, broad, disappeared on adding heavy water).

EXAMPLE 11

5-[4-(6-Hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

The procedure described in Example 3 was repeated, but using 2.2 g of ethyl 3-[4-(6-acetoxy-2-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 45), 0.8 g of thiourea, 4.5 g of sulpholane, 70 ml of ethylene glycol monomethyl ether, 8 ml of water and 4 ml of 35% w/v aqueous hydrochloric acid, to give the titl compound, melting at 249-252°C.

Nuclear Magnetic R sonance Spectrum [$(CD_3)_2SO$] δ ppm:

2.25 (6H, singlet);

2.63 (3H, singlet);

2.7-3.8 (2H, nd);

4.88 (1H, doublet of doublets, J = 4 & 9Hz);

5.11 (2H, singlet);

6.28 (1H, singlet);

7.05 (2H, doublet, J = 9Hz);

7.24 (2H, doublet, J = 9Hz);

8.3-8.7 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 12

5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-5-methylthiazolidine-2,4-dione

The procedure described in Example 3 was repeated, but using 1.17 g of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloro-2-methylpropionate (prepared as described in Preparation 46), 0.63 g of thiourea, 3 g of sulpholane, 10 ml of ethylene glycol monomethyl ether, 3 ml of water and 2 ml of 35% w/v aqueous hydrochloric acid, to give the title compound, softening at 69-72°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.40 (3H, singlet);

1.72 (3H, singlet);

1.6-2.3 (2H, nd);

2.10 (6H, singlet);

2.16 (3H, singlet);

2.62 (2H, broad triplet, J = 7Hz);

2.94 (1H, doublet, J = 14Hz);

3.24 (1H, doublet, J = 14Hz);

3.84 and 3.97 (2H, AB type, J = 9Hz);

4.40 (1H, broad singlet, disappeared on adding heavy water);

6.84 (2H, doublet, J = 9Hz);

7.13 (2H, doublet, J = 9Hz);

8.4-8.9 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 13

5-{4-[6-Hydroxy-4-(E)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

A mixture of 5 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 22 of copending USSN 644,996), 3 g of hydroxylamine hydrochloride, 50 g of methanol and 3 g of pyridine was stirred for 1 week at room temperature. At the end of this time, ethyl acetate and an aqueous solution of potassium carbonate were added. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography, eluted with a 1:1 by volume mixture of hexane and ethyl acetate, to give the title compound, softening at 84-100°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.42 (3H, singlet);

2.09 (3H, singlet);

2.18 (3H, singlet);

2.48 (3H, singlet);

3.03 (1H, doublet of doublets, J = 9 & 14Hz);

3.07 (2H, singlet);

3.43 (1H, doublet of doublets, J = 4 & 14Hz);

4.05 (2H, singlet);

4.72 (1H, doublet of doublets, J = 4 & 9Hz);

6.92 (2H, doublet, J = 9Hz);

7.21 (2H, doublet, J = 9Hz);

9.7-10.5 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 14

5-{4-[6-Hydroxy-4-(Z)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

The title compound, softening at 100-105°C, was obtained from the fraction that was eluted following the fraction containing the compound of Example 13 in the column chromatography conducted in Example 13 and using the same eluent.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.46 (3H, singlet);

2.04 (3H, singlet);

2.18 (6H, singlet);

2.58 (1H, doublet, J = 13Hz);

2.87 (1H, doublet, J = 13Hz);

3.10 (1H, doublet of doublets, J = 9 & 14Hz);

3.43 (1H, doublet of doublets, J = 4 & 14Hz);

4.01 (2H, singlet);

4.74 (1H, doublet of doublets, J = 4 & 9Hz);

6.92 (2H, doublet, J = 9Hz);

7.22 (2H, doublet, J = 9Hz);

9.4-10.6 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 15

5-{4-[6-Hydroxy-4-(Z)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

27 mg of 5-{4-[6-hydroxy-4-(E)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione (prepared as described in Example 13) was heated on an oil bath for 5 hours at 140±5°C. The reaction mixture was then subjected to high pressure liquid chromatography, which confirmed the presence of the title compound (the same compound as in Example 14).

EXAMPLE 16

5-{4-[6-Hydroxy-4-(E)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

62 mg of 5-{4-[6-hydroxy-4-(Z)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione (prepared as described in Example 14) were heated in an oil bath for 5 hours at 140±5°C. The reaction mixture was subjected to high pressure liquid chromatography, to confirm the presence of the title compound (the same compound as described in Example 13.

EXAMPLE 17

5-{4-[6-Acetoxy-4-(E)-acetoxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

A mixture of 1 g of 5-{4-[6-hydroxy-4-(E)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione (prepared as described in Example 13), 1.3 g of acetic anhydride and 10 ml of pyridine was allowed to stand for 8 days at room temperature, after which it was heated for 8 hours at 60-80°C. An aqueous solution of potassium carbonate and ethyl acetate were then added to the reaction mixture. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography, eluted with a 4:1 by volume mixture of hexane and ethyl acetate, to give the title compound, softening at 93-97°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.48 (3H, singlet);

2.07 (3H, singlet);

2.10 (3H, singlet);

2.22 (3H, singlet);

2.33 (3H, singlet);

2.42 (3H, singlet);

3.00 (1H, doublet, J=17Hz);

3.26 (1H, doublet, J=17Hz);

3.0-3.3 (1H, nd);

3.41 (1H, doublet of doublets, J=4 & 14Hz);

3.91 and 4.06 (2H, AB type, J=9Hz);

4.47 (1H, doublet of doublets, J=4 & 9Hz);

6.84 (2H, doublet, J=9Hz);

7.14 (2H, doublet, J=9Hz);

EXAMPLE 18

5-{4-[6-Benzoyloxy-4-(E)-benzoyloxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

A mixture of 1 g of 5-{4-[6-hydroxy-4-(E)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione (prepared as described in Example 13), 1.7 g of benzoyl bromide, 10 ml of pyridine and 5 ml of dimethylformamide was allowed to stand for 6 days at room temperature, after which it was heated for 8 hours at 60-80°C. An aqueous solution of potassium carbonate and ethyl acetate were then added to the reaction mixture. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography eluted with a 4:3 by volume mixture of hexane and ethyl acetate, to give the title compound, softening at 101-107°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.55 (3H, singlet);

2.14 (6H, singlet);

2.58 (3H, singlet);

2.8-3.7 (4H, nd);

3.98 and 4.12 (2H, AB type, J=9Hz);

4.45 (1H, doublet of doublets, J=4 & 9Hz);

6.84 (2H, doublet, J=9Hz);

7.14 (2H, doublet, J=9Hz);

7.3-7.8 (6H, multiplet);

7.9-8.5 (4H, multiplet).

EXAMPLE 19

5-{4-[2,5,7,8-Tetramethyl-6-nicotinoyloxy-4-(E)-nicotinoyloxyiminochroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

A mixture of 1 g of 5-{4-[6-hydroxy-4-(E)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione (prepared as described in Example 13), 1.1 g of nicotinoyl chloride hydrochloride, 12 ml of pyridine and 12 ml of dimethylformamide was allowed to stand for 6 days at room temperature, after which it was heated for 8 hours at 60-80°C. An aqueous solution of potassium carbonate and ethyl acetate were then added to the reaction mixture. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off, and the residue was purified by silica gel column chromatography eluted with a 2:3 by volume mixture of hexane and ethyl acetate, followed by preparative thin layer silica gel chromatography (developing solvent, hexane:ethyl acetate = 1:10 by volume), to give the title compound, softening at 123-130°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.56 (3H, singlet);

2.13 (3H, singlet);

2.17 (3H, singlet);

2.57 (3H, singlet);

2.8-3.7 (4H, nd);

3.99 and 4.18 (2H, AB type, J=9Hz);

4.45 (1H, doublet of doublets, J=4 & 9Hz);

6.84 (2H, doublet, J=9Hz);

7.15 (2H, doublet, J=9Hz);

7.4-7.7 (2H, multiplet);

8.3-8.7 (2H, multiplet);

8.7-9.0 (2H, multiplet);

9.2-9.6 (2H, multiplet);

10.0-11.0 (1H, broad, disappeared on adding heavy water).

EXAMPLE 20

5-{4-[7-t-Butyl-6-hydroxy-4-(E)-hydroxyimino-2-methylchroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione

The procedure described in Example 13 was repeated, but using 1.32 g of 5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione (prepared as described in Example 24 of copending EP-A 0139421), 2.0 g of hydroxylamine hydrochloride, 0.5 ml of pyridine and 20 ml of methanol, to give the title compound as colourless crystals, melting at 235-237°C (with decomposition).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.40 (12H, singlet);

2.6-4.0 (1H, broad, disappeared on adding heavy water);

2.98 (2H, singlet);

3.10 (1H, doublet of doublets, J=9 & 14Hz);

3.43 (1H, doublet of doublets, J=4 & 14Hz);

4.05 (2H, singlet);

4.74 (1H, doublet of doublets, J=4 & 9Hz);

6.73 (1H, singlet);

6.95 (2H, doublet, J=9Hz);

7.2-8.5 (1H, broad, disappeared on adding heavy water);

7.25 (2H, doublet, J=9Hz);

7.30 (1H, singlet);

9.7-10.6 (1H, broad disappeared on adding heavy water).

EXAMPLE 21

5-{4-[6-Hydroxy-4-(E)-hydroxyimino-2-methyl-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

The procedure described in Example 13 was repeated, but using 1.0 g of 5-{4-[6-hydroxy-2-methyl-4-oxo-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione (prepared as described in Example 7), 0.26 g of hydroxylamine hydrochloride, 0.3 g of pyridine and 10 ml of methanol, to give the title compound as a white powder, softening at 115-120°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

0.76 (9H, singlet);

1.40 (9H, singlet);

2.00 (2H, singlet);

2.5-3.6 (1H, broad, disappeared on adding heavy water);

2.98 (2H, singlet);

3.09 (1H, doublet of doublets, J=9 & 15Hz);

3.44 (1H, doublet of doublets, J=4 & 15Hz);

4.03 (2H, singlet);

4.76 (1H, doublet of doublets, J=4 & 9Hz);

6.75 (1H, singlet);

6.93 (2H, doublet, J=9Hz);

7.22 (2H, doublet, J=9Hz);

7.25 (1H, singlet);

7.5-8.4 (1H, broad, disappeared on adding heavy water).

EXAMPLE 22

5-{4-[6-Hydroxy-4-(E)-hydroxyimino-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

The procedure described in Example 13 was repeated, but using 155 mg of 5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (prepared

as described in Example 1), 600 mg of hydroxylamine hydrochloride, 4 ml of ethanol and 6 ml of pyridine, to giv the title compound, softening at 77-80°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

0.97 (6H, doublet, J=6Hz);

1.6-2.3 (1H, nd);

1.78 (2H, doublet, J=6Hz);

2.11 (3H, singlet);

2.18 (3H, singlet);

2.46 (3H, singlet);

2.7-3.7 (1H, broad, disappeared on adding heavy water);

2.8-3.2 (1H, nd);

3.09 (2H, singlet);

3.43 (1H, doublet of doublets, J=4 & 14Hz);

4.05 (2H, AB type, J=10Hz);

4.72 (1H, doublet of doublets, J=4 & 9Hz);

6.91 (2H, doublet, J=9Hz);

7.22 (2H, doublet, J=9Hz);

9.8-10.5 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 23

5-{4-[2-(3,7-Dimethyloctyl)-6-hydroxy-4-(E)-hydroxyimino-5,7,8-trimethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

The procedure described in Example 13 was repeated, but using 150 mg of 5-{4-[2-(3,7-dimethyloctyl)-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione (prepared as described in Example 8), 36 mg of hydroxylamine hydrochloride, 41 mg of pyridine and 2 ml of methanol, to give the title compound as a slightly yellow powder, softening at 55-60°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.83 (9H, doublet, J=7Hz);

1.0-2.0 (12H, multiplet);

2.10 (3H, singlet);

2.18 (3H, singlet);

2.41 (3H, singlet);

2.9-3.2 (1H, nd);

2.92 (1H, doublet, J=17Hz);

3.2-3.55 (1H, nd);

3.23 (1H, doublet, J=17Hz);

3.94 (2H, singlet);

4.3-4.8 (1H, nd);

4.46 (1H, doublet or doublets, J=4 & 10Hz);

6.83 (2H, doublet, J=9Hz);

7.15 (2H, doublet, J=9Hz);

7.8-8.9 (2H, broad, disappeared on adding heavy water).

EXAMPLE 24

5-[4-(6-Hydroxy-2,5,7,8-tetramethyl-4-(E)-methoxyiminochroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione

A mixture of 1g of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 22 of copending EP-A 0139421), 0.6 g of methoxyamine hydrochloride and 5 g of methanol was allowed to stand for 10 days at room temperature. At the end of this time, ethyl acetate and an aqueous solution of potassium carbonate were added. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography eluted with a 3:1 by volume mixture of hexane and ethyl acetate, to give the title compound, softening at 72-76°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.41 (3H, singlet);

2.08 (3H, singlet);

2.17 (3H, singlet);

2.50 (3H, singlet);

2.88 & 3.08 (2H, AB type, J=17Hz);

3.00 (1H, doublet of doublets, J=9 & 14Hz);

3.42 (1H, doublet of doublets, J=4 & 14Hz);

3.92 (2H, singlet);

3.96 (3H, singlet);

4.2-4.9 (1H, broad);

4.45 (1H, doublet of doublets, J=4 & 9Hz);

6.83 (2H, doublet, J=9Hz):

7.12 (2H, doublet, J=9Hz).

EXAMPLE 25

5-{4-[4-(E)-Benzyloxyimino-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

A mixture of 1 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 22 of copending EP-A 0139421), 1.2 g of benzyloxylamine hydrochloride and 10 g of methanol was allowed to stand for 7 days at room temperature. At the end of this time, ethyl acetate and an aqueous solution of potassium carbonate were added. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography eluted with a 3:1 by volume mixture of hexane and ethyl acetate, to give the title compound, softening at 64-69°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.40 (3H, singlet);

2.06 (3H, singlet);

2.16 (3H, singlet);

2.41 (3H, singlet);

2.92 & 3.18 (2H, AB type, J=17Hz);

3.02 (1H, doublet of doublets, J=9 & 14Hz);

3.42 (1H, doublet of doublets, J=4 & 14Hz);

3.90 (2H, singlet);

4.43 (1H, doublet of doublets, J=4 & 9Hz);

5.19 (2H, singlet);

6.82 (2H, doublet, J=9Hz);

7.11 (2H, doublet, J=9Hz);

7.2-7.5 (5H, multiplet).

EXAMPLE 26

5-{4-[4-(E)-t-Butoxycarbonylmethoxyimino-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

A mixture of 1 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 22 of copending EP-A 0139421), 2.1 g of t-butoxycarbonylmethoxylammonium p-toluenesulphonate, 5 g of methanol and 0.6 g of pyridine was allowed to stand for 7 days at room temperature. At the end of this time, ethyl acetate and an aqueous solution of potassium carbonate were added. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography eluted with a 3:1 by volume mixture of hexane and ethyl acetate, to give the title compound, softening at 76-80°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm

1.44 (3H, singlet);

1.49 (9H, singlet);

2.07 (3H, singlet);

2.17 (3H, singlet);

2.43 (3H, singlet);

3.02 (1H, doublet of doublets, J = 9 & 14 Hz);

3.08 (2H, AB type, J = 17Hz);

3.42 (1H, doublet of doublets, J = 4 & 14Hz);

3.96 (2H, singlet);

4.43 (1H, doublet of doublets, J = 4 & 9Hz);

4.57 (2H singlet);

4.9-6.1 (2H, broad, disappeared on adding heavy water);

6.84 (2H doublet, J = 9Hz);

7.10 (2H, doublet, J = 9Hz).

EXAMPLE 27

(a) 5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one and (b) 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (Step A5)

A mixture of 9.6 g of ethyl 3-[4-6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 51),1.8 g of thiourea and 11 ml of sulpholane was heated at 115-120°C for 80 minutes under a stream of nitrogen. A mixture of 90 ml of acetic acid, 30 ml of concentrated hydrochloric acid and 15 ml of water was then added to the reaction mixture, which was then heated at 85-90°C for a further 12 hours. 27 g of sodium bicarbonate were added to the reaction mixture, and, after the generation of carbon dioxide gas had ceased, the solvent was distilled off. A mixture of 10 parts by volume of benzene and 1 part of ethyl acetate was added to the crude residue, and the resulting solution was washed with a 1:1 by volum mixture of a saturated aqueous solution of sodium bicarbonate and water. A white powdery product was collected by filtration, washed with water and recrystallized from acetone to give the title compound (a), melting at 205-207°C.

Nuclear Magnetic Resonance Spectrum [$DCON(CD_3)_2$ + D_2O] δ ppm:

1.37 (3H, singlet);

about 2 (2H, multiplet);

2.02 (3H, singlet);

2.14 (6H, singlet);

2.3-3.1 (adsorption signal of solvent);

3.42 (1H, doublet of doublets, J = 15 & 4.5Hz);

4.60 (1H, doublet of doublets, J = 9 & 4.5Hz);

6.93 (2H, doublet, J = 9Hz);

7.23 (2H, doublet, J = 9Hz).

The organic layer which was obtained after removal of the above white powder was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off and the resulting crude residue was purified by silica gel column chromatography. After elution with a 10:1 by volume mixture of benzene and ethyl acetate, the title compound (b) was obtained as a powder, melting at 184-186°C, from the next elution with a 10:1.4 by volume mixture of benzene and ethyl acetate.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.39 (3H, singlet);

about 2 (2H, multiplet);

2.02 (3H, singlet);

2.09 (3H, singlet);

2.13 (3H, singlet);

2.63 (2H, broad triplet, J = 6Hz);

3.07 (1H, doublet of doublets, J = 15 & 9Hz);

3.41 (1H, doublet of doublets, J = 15 & 4.5Hz);

3.97 (2H, AB type, J = 9Hz);

4.70 (1H, doublet of doublets, J = 9 & 4.5Hz);

6.90 (2H, doublet, J = 9Hz);

7.21 (2H, doublet, J = 9Hz).

EXAMPLE 28

5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (Step A5)

A mixture of 9.6 g of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylcroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 51), 1.8 g of thiourea and 11 ml of sulpholane was heated for 3.5 hours at 120°C under a nitrogen stream. 100 ml of ethylene glycol monomethyl ether and 70 ml of 10% w/v aqueous hydrochloric acid were then added to the reaction mixture, after which it was heated under reflux for 12 hours. The product was then purified as described in Example 27, to give the title compound. The melting point and nuclear magnetic resonance spectrum of this compound accorded with those of the compound obtained in Example 27(b).

EXAMPLE 29

5-[4-(7-t-Butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (Step A5)

Following the procedure described in Example 28, a mixture of 1.43 g of ethyl 3-[4-(6-acetoxy-7-t-butyl-2-methylchroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 59), 430 mg of thiourea and 5 ml of solpholane was heated for 3.5 hours at 120°C. 15 ml of ethylene glycol monomethyl ether and 10 ml of 10% w/v aqueous hydrochloric acid were then added to the reaction mixture, after which it was heated under reflux for 13 hours. The product was then separated and purified as described in Example 27, to give the title compound as a slightly yellow powder.

Rf value on silica gel thin layer chromatography = 0.31 (developing solvent, benzene:ethyl acetate = 5:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.37 (9H, singlet);

1.43 (3H, singlet);

1.63-2.30 (2H, multiplet);

2.67 (2H, broad triplet, J = 7Hz);

3.07 (1H, doublet of doublets, J = 9 & 15Hz);

3.45 (1H, doublet of doublets, J = 4 & 15Hz);

3.87 & 3.97 (2H, AB type, J = 9Hz);

4.48 (1H, doublet of doublets, J = 4 & 9Hz);

4.62 (1H, broad singlet, disappeared on adding heavy water);

6.41 (1H, singlet);

6.78 (1H, singlet);

6.88 (2H, doublet, J = 9Hz);

7.15 (2H, doublet, J = 9Hz);

8.40-8.93 (1H, broad, disappeared on adding heavy water).

EXAMPLE 30

5-[4-(4,6-Dihydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (Step H1)

450 mg of sodium borohydride were added to a mixture of 278 mg of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 22 of copending EP-A 0139421) and 9 ml of methanol, and the mixture was stirred for 2 hours at room temperature, after which a 1% w/v aqueous solution of acetic acid was added and th mixture was neutralized with an aqueous solution of potassium carbonate. It was then extracted with ethyl acetate. The ethyl acetate extract was washed with water and dried over anhydrous sodium sulphate. The ethyl acetate was distilled from the extract under reduced pressure and the resulting residue was purified by silica gel column chromatography, using a 5:3 by volume mixture of hexane and ethyl acetate as eluent, to give the title compound, melting at 102-118°C.

Nuclear Magnetic Resonance Spectrum

[$(CD_3)_2CO$ + D_2O] δ ppm:

1.52 (3H, singlet);

2.01 (3H, singlet);

2.13 (3H, singlet);

2.29 (3H, singlet);

1.9-2.5 (1H, nd);

2.9-3.6 (2H, multiplet);

4.03 (2H, singlet);

3.9-4.5 (1H, nd);

4.6-5.1 (2H, multiplet);

6.7-7.4 (4H, nd).

EXAMPLE 31

(a) 2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)-phenoxymethyl]-2,5,7,8-tetramethylchroman-6-yl hydrogen succinate

A mixture of 1.0 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 28), 0.31 g of succinic anhydride and 1 ml of pyridine was allowed to stand overnight at room temperature. The reaction mixture was then washed 3 times, each time with 10 ml of cyclohexane, and the insoluble residue obtained was purified by silica gel column chromatography (eluted by mixtures of benzene and ethyl acetate ranging from 5:1 to 1:1) to give the title compound melting at 197-202°C.

Nuclear Magnetic Resonance Spectrum - (pentadeuterated pyridine) δ ppm:

1.36 (3H, singlet);

1.5-2.3 (2H, multiplet);

2.10 (6H, singlet);

2.14 (3H, singlet);

2.5 (2H, broad triplet, J = 6Hz);

2.73-3.35 (5H, multiplet);

3.60 (1H, doublet of doublets, J = 4 & 15Hz);

3.95 & 4.05 (2H, AB-type, J = 9Hz);

4.90 (1H, doublet of doublets, J = 4 & 9Hz);

6.98 (2H, doublet, J = 9Hz);

7.30 (2H, doublet, J = 9Hz).

(b) 2-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenoxymethyl]-2,5,7,8-tetramethylchroman-6-yl hydrogen succinate sodium salt

1 ml of a 2.5% w/v methanolic solution of sodium methoxide was added to a suspension of 248 mg of the compound obtained as described in (a) above in 100 ml of methanol at room temperature. Insoluble matter was filtered off, and then the methanol was distilled off under reduced pressure and the residue was washed with diethyl ether to give the title compound, melting at 178-180°C.

EXAMPLE 32

5-[4-(6-Hydroxy-2,5,7,8-tetramethyl-2H-chromen-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

A mixture of 140 mg of 5-[4-(4,6-dihydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 30), 10 mg of p-toluenesulphonic acid, 10 ml of benzene and 0.5 ml of dimethylformamide was heated under reflux for 1 hour. The reaction solution was cooled, washed with a saturated aqueous solution of sodium bicarbonate and then with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography eluted with a 4:1 by volume mixture of benzene and ethyl acetate, to give the title compound, softening at 173-176°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$) δ ppm:

1.50 (3H, singlet);

2.02 (3H, singlet);

2.12 (3H, singlet);

2.18 (3H, singlet);

3.06 (1H, doublet of doublets, J = 9 & 14Hz);

3.40 (1H, doublet of doublets, J = 4 & 14Hz);

3.94 (1H, doublet, J = 10Hz);

4.05 (1H, doublet, J = 10Hz);

4.70 (1H, doublet of doublets, J = 4 & 9Hz);

5.75 (1H, doublet, J = 10Hz);

6.72 (1H, doublet, J = 10Hz);

6.85 (2H, doublet, J = 9Hz);

7.19 (2H, doublet, J = 9Hz).

EXAMPLE 33

5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (Step H3)

Following the procedure described in Preparation 58, 120 mg of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-2H-chromen-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 32) were dissolved in 4 ml of methanol and, in the presence of 40 mg of 10% w/w palladium-on-carbon, it was reduced under 3-5 atmospheres - (about 3-5 bars) pressure of hydrogen, to give the title compound. The melting point and nuclear magnetic resonance spectrum of this compound accorded with those of the compound obtained in Example 27(b).

EXAMPLE 34

5-[4-(4-Carboxymethoxyimino-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione

A mixture of 0.7 g of 5-[4-(4-t-butoxycarbonylmethoxyimino-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (prepared as described in Example 26) and 7 ml of a 4N dioxane solution of hydrogen chloride was allowed to stand at room temperature for 15 hours. At the end of this time, the solvent was distilled off and the residue was washed with warm water to give the title compound, softening at 75-85°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:

1.33 (3H, singlet);

1.98 (3H, singlet);

2.09 (3H, singlet);

2.34 (3H, singlet);

2.9-3.5 (2H, multiplet);

3.0 (2H, singlet);

4.02 (2H, singlet);

4.65 (2H, singlet);

4.84 (1H, doublet of doublets, J = 4 & 9Hz);

6.90 (2H, doublet, J = 9Hz);

7.17 (2H, doublet, J = 9Hz);

7.55-7.95 (1H, broad, disappeared on adding heavy water).

EXAMPLE 35

2-Methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethyl-4-oxochroman-6-yloxy}acetate

A mixture of 13 g of ethyl 3-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 64), 2.6 g of thiourea and 15 ml of sulpholane was heated under a nitrogen stream at 120-130°C for 5 hours. 30 ml of 2N aqueous hydrochloric acid and 60 ml of 2-methoxyethanol were added to the resulting mixture, which was then heated at 110°C for 3 hours. The reaction mixture was then poured into water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled from the dried extract, and the residue was purified by silica gel column chromatography (eluted with a 4:1 by volume mixture of benzene and ethyl acetate) to give the title compound.

Rf value on silica gel thin layer chromatography = 0.14 (developing solvent, benzene:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.50 (3H, singlet);

2.10 (3H, singlet);

2.26 (3H, singlet);

2.45-2.8 (1H, nd);

2.56 (3H, singlet);

2.9-3.25 (1H, nd);

3.07 (1H, doublet, J=16Hz);

3.40 (3H, singlet);

3.4-3.6 (1H, nd);

3.6-3.75 (2H, multiplet);

3.98 & 4.11 (2H, AB type, J=10Hz);

4.3-4.45 (2H, multiplet);

4.34 (2H, singlet);

4.45-4.6 (1H, nd);

6.85 (2H, doublet, J/9Hz);

7.16 (2H, doublet, J=9Hz);

8.7-9.3 (1H, broad).

EXAMPLE 36

5-[4-(6-Ethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2, 4-dione

The title compound, melting at 56-60°C, was obtained from 5.1 g of ethyl 2-chloro-3[4-(6-ethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-propionate (prepared as described in Preparation 65), 1 g of thiourea, 6 ml of sulpholane, 16 ml of 2N aqueous hydrochloric acid and 5 ml of 2-methoxyethanol, according to the same procedure as described in Example 35.

Mass spectrum (m/e): 469 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.39 (3H, triplet, J=7Hz);

1.41 (3H, singlet);

1.7-2.1 (2H, nd);

2.07 (3H, singlet);

2.14 (3H, singlet);

2.17 (3H, singlet);

2.61 (2H, broad triplet, J=7Hz);

3.05 (1H, doublet of doublets, J=10 & 14Hz);

3.45 (1H, doublet of doublets, J=4 & 14Hz);

3.72 (2H, quartet, J=7Hz);

3.87 & 3.97 (2H, AB type, J=9Hz);

4.47 (1H, doublet of doublets, J=4 & 10Hz);

6.87 (2H, doublet, J=9Hz);

7.14 (2H, doublet, J=9Hz);

8.6-8.8 (1H, broad, disappeared on adding heavy water).

EXAMPLE 37

2-Methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-4-hydroxy-2,5,7,8-tetramethylchroman-6-yloxy}acetate

1.5 g of sodium borohydride were added, whilst ice-cooling, to a mixture of 1.2 g of 2-methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethyl-4-oxochroman-6-yloxy}acetate (prepared as described in Example 35) and 20 ml of methanol, and the mixture was stirred for 60 minutes. The reaction mixture was then poured into ice-water, neutralized with 10% w/v aqueous hydrochloric acid, and then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure to give the title compound as a pale yellow powder.

Rf valu on silica gel thin layer chromatography = 0.20 (developing solvent, benezene:ethyl acetate = 1:1 by volum).

Mass spectrum (m/e) : 573 (M^+).

EXAMPLE 38

Methyl α-{2-[4-(2, 4-dioxothiazolidin-5-ylmethyl)-phenoxymethyl]-2,5,7,8-tetramethyl-2H-chromen-6-yloxy}acetate

A mixture of 970 mg of 2-methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-4-hydroxy-2,5,7,8-tetramethylchroman-6-yloxy}acetate (prepared as described in Example 37), 50 mg of p-toluenesulphonic acid, 10 ml of benzene and 1 ml of dioxane was heated under reflux in a nitrogen stream for 60 minutes. The reaction mixture was then washed with a 5% w/v aqueous solution of sodium bicarbonate and then with water, and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluted with a 7:3 by volume mixture of benzene and ethyl acetate), to give the title compound.

Rf value on silica gel thin layer chromatography = 0.74 (developing solvent, benzene:ethyl acetate = 1:1 by volume).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.51 (3H, singlet);

2.01 (3H, singlet);

2.14 (3H, singlet);

2.22 (3H, singlet);

3.07 (1H, doublet of doublets, J=9 & 14Hz);

3.42 (1H, doublet of doublets, J=4 & 14Hz);

3.74 (3H, singlet);

4.03 (2H, singlet);

4.32 (2H, singlet);

4.73 (1H, doublet of doublets, J=4 & 9Hz);

5.80 (1H, doublet, J=10Hz);

6.70 (1H, doublet, J=10Hz);

6.86 (2H, doublet, J=9Hz);

7.20 (2H, doublet, J=9Hz).

EXAMPLE 39

2-Methoxyethyl α{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethyl-2H-chromen-6-yloxy}acetate

The title compound was obtained from the fraction eluted after the one giving the methyl ester in the column chromatography described in Example 38, using the same eluent.

Rf value on silica gel thin layer chromatography = 0.59 (developing solvent, benzene:ethyl acetate = 1:1 by volume).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.52 (3H, singlet);

2.02 (3H, singlet);

2.16 (3H, singlet);

2.23 (3H, singlet);

3.09 (1H, doublet of doublets, J=9 & 15Hz);

3.30-3.60 (1H, nd);

3.32 (3H, singlet);

3.5-3.7 (2H, multiplet);

4.04 (2H, singlet);

4.25-4.45 (2H, multiplet);

4.35 (2H, singlet);

4.75 (1H, doublet of doublets, J=4 & 9Hz);

5.82 (1H, doublet, J=10Hz);

6.72 (1H, doublet, J=10Hz);

6.88 (2H, doublet, J=9Hz);

7.21 (2H, doubl t, J=9Hz).

EXAMPLE 40

5-{4-[6-(2-Hydroxyethoxy)-2,5,7,8-tetramethyl-2H-chromen-2-ylmethoxy]benzyl}thiazolidine-2,4-dione

The title compound was obtained from the fraction eluted after the one giving the 2-methoxyethyl ester in the silica gel column chromatography described in Example 39, using the same eluent.

Rf value on silica gel thin layer chromatography = 0.44 (developing solvent, benzene:ethyl acetate = 1:1 by volume).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.51 (3H, singlet);

2.01 (3H, singlet);

2.15 (3H, singlet);

2.21 (3H, singlet);

3.08 (1H, doublet of doublets, J=9 & 14Hz);

3.42 (1H, doublet of doublets, J=4 & 14Hz);

3.6-3.95 (4H, multiplet);

4.03 (2H, singlet);

4.74 (1H, doublet of doublets, J=4 & 9Hz);

5.78 (1H, doublet, J=10Hz);

6.71 (1H, doublet, J=10Hz);

6.88 (2H, doublet, J=9Hz);

7.21 (2H, doublet, J=9Hz).

EXAMPLE 41

2-Methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethylchroman-6-yloxy}acetate

Using Paar's hydrogenation apparatus, a mixture of 260 mg of 2-methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethyl-2 H-chromen-6-yloxy}acetate (prepared as described in Example 39), 300 mg of 10% w/v palladium-on-carbon and 50 ml of ethanol was stirred for 10 hours under a hydrogen pressure of 3-5 atmospheres. The palladium-on-carbon was then filtered off, and the filtrate was condensed by evaporation under reduced pressure, to give the title compound as a colourless oily substance.

Rf value on silica gel thin layer chromatography = 0.34 (developing solvent, benzene:ethyl acetate = 2:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.40 (3H, singlet);

1.75-2.15 (2H, nd);

2.06 (3H, singlet);

2.14 (3H, singlet);

2.18 (3H, singlet);

2.61 (2H, broad triplet, J=7Hz);

3.05 (1H, doublet of doublets, J=9 & 14 Hz);

3.35-3.8 (3H, nd);

3.39 (3H, singlet);

3.86 & 3.96 (2H, AB type, J=10Hz);

4.25-4.6 (3H, nd);

4.34 (2H, singlet);

6.87 (2H, doublet, J=9Hz);

7.15 (2H, doublet, J=9Hz);

8.35-8.8 (1H, broad, disappeared on adding heavy water).

EXAMPLE 42

5-{4-[6-(2-Hydroxyethoxy)-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione

Following the same procedure as described in Example 41, 0.35 g of 5-{4-[6-(2-hydroxyethoxy)-2,5,7,8-tetramethyl-2H-chromen-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione (prepared as described in Example 40), 0.3 g of 10% w/w palladium on activated carbon and 10 ml of ethanol gave the title compound.

Rf value on silica gel thin layer chromatography = 0.45 (developing solvent, benzene:ethyl acetate = 1:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.41 (3H, singlet);

1.71-2.2 (2H, nd);

2.07 (3H, singlet);

2.13 (3H, singlet);

2.18 (3H, singlet);

2.61 (2H, broad triplet, J = 7Hz);

3.05 (1H, doublet of doublets, J = 9 & 14Hz);

3.44 (1H, doublet of doublets, J = 4 & 14Hz);

3.7-4.1 (6H, multiplet);

4.47 (1H, doublet of doublets, J = 4 & 9Hz);

4.8-5.2 (2H, broad);

6.87 (2H, doublet, J = 9Hz);

7.14 (2H, doublet, J = 9Hz).

EXAMPLE 43

Ethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenoxymethyl]-2,5,7,8-tetramethyl-4-oxochroman-6-yloxy}acetate

A mixture of 0.5 g of α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethyl-4-oxochroman-6-yloxy}acetic acid - (obtained as described in Example 59), 0.5 ml of a 4N dioxane solution of hydrogen chloride and 5 ml of ethanol was allowed to stand overnight at room temperature. The reaction mixture was then poured into water and the solution was neutralized with sodium bicarbonate and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off, and the residue was subjected to preparative silica gel thin layer chromatography - (developing solvent, benzene:ethyl acetate = 7:3 by volume) to obtain the title compound.

Rf value on silica gel thin layer chromatography = 0.70 (developing solvent, benzene:ethyl acetate = 1:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.33 (3H, triplet, J = 7Hz);

1.50 (3H, singlet);

2.10 (3H singlet);

2.26 (3H, singlet);

2.57 (3H, singlet);

2.55-2.8 (1H, nd);

3.06 (1H, doublet, J = 16Hz);

3.07 (1H, doublet of doublets, J = 9 & 14Hz);

3.45 (1H, doublet of doublets, J = 4 & 14Hz);

4.00 & 4.11 (2H, AB type, J = 10Hz);

4.29 (2H, singlet);

4.31 (2H, quartet, J = 7Hz);

4.48 (1H, doublet of doublets, J = 4 & 9Hz);

6.85 (2H, doublet, J = 9Hz);

7.16 (2H, doublet, J = 9Hz);

8.3-8.9 (1H, broad).

EXAMPLE 44

t-Butyl α-{5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate

0.87 g of t-butyl bromoacetate was added dropwise, whilst ice-cooling, to a mixture of 1 g of 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl] thiazolidine-2,4-dione [prepared as described in Example 3(b) of copending EP-A 0139421], 0.43 g of anhydrous potassium carbonate, and 8 ml of acetone. The resulting mixture was stirred for 2 hours at room temperature and then allowed to stand for 2 days, also at room temperature. The reaction mixture was then poured into ice-water and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous

sodium sulphate. The solvent was distilled off and the residue was subjected to silica gel column chromatography (eluent:benzene) to give the title compound.

Rf value on silica gel thin layer chromatography = 0.6 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.41 (3H, singlet);

1.47 (9H, singlet);

1.7-2.1 (2H, nd);

1.98 (3H, singlet);

2.02 (3H, singlet);

2.07 (3H, singlet);

2.30 (3H, singlet);

2.82 (2H, broad triplet, J = 7Hz);

2.98 (1H, doublet of doublets, J = 10 & 14Hz);

3.55 (1H, doublet of doublets, J = 4 & 14Hz);

3.86 & 3.97 (2H, AB type, J = 9Hz);

4.19 (2H, singlet);

4.45 (1H, doublet of doublets, J = 4 & 10Hz);

6.86 (2H, doublet J = 9Hz);

7.15 (2H, doublet, J = 9Hz).

EXAMPLE 45

Methyl α-{5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate

Following the procedure described in Example 44, 2.4 g of 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione [prepared as described in Example 3(b) of copending EP-A 0139421], 1.5 g of methyl bromoacetate, 1.5 g of potassium carbonate and 25 ml of acetone gave the title compound as a colourless oil.

Rf value on silica gel thin layer chromatography = 0.26 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.42 (3H, singlet);

1.8-2.25 (2H, nd);

1.98 (3H, singlet);

2.02 (3H, singlet);

2.08 (3H, singlet);

2.30 (3H, singlet);

2.84 (2H, broad triplet, J = 7Hz);

3.01 (1H, doublet or doublets, J = 10 & 14Hz);

3.54 (1H, doublet or doublets, J = 4.5 & 14Hz);

3.75 (3H, singlet);

3.87 & 4.00 (2H, AB type, J = 9Hz);

4.31 (2H, singlet);

4.50 (1H, doublet of doublets, J = 4.5 & 10Hz);

6.89 (2H, doublet, J = 9Hz);

7.17 (2H, doublet, J = 9Hz).

EXAMPLE 46

t-Butyl α-{5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate

Following the procedure described in Example 44, 1 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione [prepared as described in Example 27(b)], 0.47 g of anhydrous potassium carbonate, 0.93 g of t-butyl bromoacetate and 8 ml of acetone gave the title compound.

Rf value on silica gel thin layer chromatography = 0.52 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.42 (3H, singlet);

1.48 (9H, singlet);

1.7-2.15 (2H, nd);

2.11 (6H, singlet);

2.16 (3H, singlet);

2.64 (2H, broad triplet, J = 7Hz);

2.99 (1H, doublet of doublets, J = 10 & 14Hz);

3.56 (1H, doublet of doublets, J = 4 & 14Hz);

3.85 & 3.98 (2H, AB type, J = 9Hz);

4.21 (2H, singlet);

4.24 (1H, singlet);

4.46 (1H, doublet of doublets, J = 4 & 10Hz);

6.88 (2H, doublet, J = 9Hz);

7.15 (2H, doublet), J = 9Hz).

EXAMPLE 47

Di-t-butyl α,α'-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetate

1.9 g of t-butyl bromoacetate was added dropwise, whilst ice-cooling, to a mixture of 1 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione [prepared as described in Example 27(b)], 0.94 g of anhydrous potassium carbonate and 10 ml of acetone. The resulting mixture was stirred for 2 days at room temperature. The reaction mixture was then poured into ice-water and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was subjected to silica gel column chromatography (eluent, benzene:ethyl acetate = 20:1 by volume) to give the title compound.

Rf valu on silica gel thin layer chromatography = 0.54 (developing solvent, cyclohexane:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.44 (9H, singlet);

1.48 (12H, singlet);

1.54 (9H, singlet);

1.8-2.1 (2H, nd);

2.07 (3H, singlet);

2.16 (3H, singlet);

2.20 (3H, singlet);

2.5-2.7 (2H, multiplet);

2.9-3.15 (2H, multiplet);

3.24 (2H, singlet);

3.93 (2H, broad singlet);

4.13 (2H, singlet);

4.17 (2H, singlet);

6.85 (2H, broad doublet, J = 9Hz);

7.15 (2H, broad doublet, J = 9Hz).

Mass Spectrum (m/e) : 783 (M^+).

EXAMPLE 48

t-Butyl α-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate

In the column chromatography separation process described in Example 47, the title compound was obtained from the fractions eluted after those giving the t-butyl ester of Example 47, using the same eluent.

Rf value on silica gel thin layer chromatography = 0.42 (developing solvent, cyclohexane:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm.

1.42 (3H, singlet);

1.48 (9H, singlet);

1.54 (9H, singlet);

1.7-2.1 (2H, nd);

2.06 (3H, singlet);

2.15 (3H, singlet);

2.19 (3H, singlet);

2.61 (2H, broad triplet, J = 7Hz);

2.99 (1H, doublet of doublets, J = 10 & 14Hz);

3.56 (1H, doublet of doublets J = 4 & 14Hz);

3.87 & 3.96 (2H, AB type, J = 9Hz);

4.17 (2H, singlet);

4.20 (2H, singlet);

4.46 (1H, doublet of doublets, J = 4 & 10Hz);

6.87 (2H, doublet, J = 9Hz);

7.15 (2H, doublet, J = 9Hz).

Mass Spectrum (m/e) : 669 (M^+).

EXAMPLE 49

t-Butyl-α-{5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate

Following the procedure described in Example 44, 1 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (prepared as described in Example 22 of copending EP-A 0139421), 0.45 g of anhydrous potassium carbonate, 0.9 g of t-butyl bromoacetate and 8 ml of acetone gave the title compound, softening at 170-180°C.

Nuclear Magnetic Resonance Spectrum $[(CD_3)_2CO]$ δ ppm:

1.46 (9H, singlet);

1.50 (3H, singlet);

2.10 (3H, singlet);

2.22 (3H, singlet);

2.5-2.8 (1H, nd);

2.54 (3H, singlet);

3.03 (1H, doublet of doublets, J = 10 & 14Hz);

3.04 (1H, doublet, J = 16Hz);

3.53 (1H, doublet of doublets, J = 4 & 14Hz);

4.16 (2H, singlet);

4.22 (2H, singlet);

4.82 (1H, doublet of doublets, J = 4 & 10Hz);

6.96 (2H, doublet, J = 9Hz);

7.25 (2H, doublet, J = 9Hz).

EXAMPLE 50

Di-t-butyl α,α'-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)-benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetate

Following the procedure described in Example 47, 1.5 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (prepared as described in Example 22 of copending EP-A 0139421), 1.3 g of anhydrous potassium carbonate, 5.4 g of t-butyl bromoacetate and 10 ml of acetone gave the title compound.

Rf value on silica gel thin layer chromatography = 0.57 (developing solvent, cyclohexane:ethyl acetate = 7:3 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.42 (9H, singlet);

1.46 (9H, singlet);

1.48 (3H, singlet);

1.52 (9H, singlet);

2.10 (3H, singlet);

2.26 (3H, singlet);

2.55-3.20 (4H, nd);

2.56 (3H, singlet);

3.23 (2H, singlet);

3.97 & 4.08 (2H, AB type, J=10Hz);

4.12 (2H, singlet);

4.16 (2H, singlet);

6.82 (2H, doublet, J=9Hz);

7.15 (2H, doublet, J=9Hz).

Mass spectrum (m/e): 797 (M^+).

EXAMPLE 51

t-Butyl α-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate

From the fraction eluted following the one giving di-t-butyl α,α'-{5-[4-(6-t-butyloxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetate as described in Example 50, the title compound was obtained, using the same eluent.

Rf value on silica gel thin layer chromatography = 0.46 (developing solvent, cyclohexane:ethyl acetate = 7:3 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.47 (9H, singlet);

1.50 (3H, singlet);

1.53 (9H, singlet);

2.10 (3H, singlet);

2.26 (3H, singlet);

2.56 (3H, singlet);

2.6-3.2 (3H, nd);

3.57 (1H, doublet of doublets, J=4 & 14Hz);

3.98 & 4.11 (2H, AB type, J=10Hz);

4.17 (2H, singlet);

4.20 (2H, singlet);

4.47 (1H, doublet of doublets, J=4 & 10Hz);

6.86 (2H, doublet, J=9Hz);

7.16 (2H, doublet, J=9Hz).

Mass spectrum (m/e): 683 (M^+).

EXAMPLE 52

3-Ethyl-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione

Following the procedure described in Example 44, 0.58 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4,-dione [prepared as described in Example 27(b)], 0.27 g of anhydrous potassium carbonate, 0.6 g of ethyl iodide and 5 ml of acetone gave the title compound.

Rf value on silica gel thin layer chromatography = 0.30 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.09 (3H, triplet, J=7Hz);

1.40 (3H, singlet);

1.7-2.2 (2H, nd);

2.09 (6H, singlet);

2.14 (3H, singlet);

2.62 (2H, broad triplet, J=7Hz);

3.02 (1H, doublet of doublets, J=9 & 14Hz);

3.25-3.5 (1H, nd);

3.59 (2H, quartet, J=7Hz);

3.83 & 3.96 (2H, AB type, J = 10Hz);

4.23 (1H, singlet, disappeared on adding heavy water);

4.36 (1H, doublet of doublets, J = 4 & 9Hz);

6.84 (2H, doublet, J = 9Hz);

7.11 (2H, doublet, J = 9Hz).

EXAMPLE 53

t-Butyl α-{5-[4-(6-hydroxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate

A mixture of 0.5 g of t-butyl α-{5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)-benzyl]-2,4-dioxothiazolidin-3-yl}acetate (prepared as described in Example 49), 0.25 g of hydroxylamine hydrochloride, 0.25 g of pyridine and 5 ml of methanol was allowed to stand at 25-30°C for 2 days. Ethyl acetate and an aqueous solution of potassium carbonate were added to the mixture, and the organic layer was separated. The organic layer was dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was subjected to silica gel column chromatography - (eluted with a 9:1 by volume mixture of benzene and ethyl acetate) to obtain the title compound.

Rf value on silica gel thin layer chromatography = 0.55 (developing solvent, benzene:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.42 (3H, singlet);

1.45 (9H, singlet);

2.07 (3H, singlet);

2.17 (3H, singlet);

2.48 (3H, singlet);

3.03 (1H, doublet of doublets, J = 10 & 13.5Hz);

3.07 (2H, singlet);

3.55 (1H, doublet of doublets, J = 4 & 13.5Hz);

4.06 (2H, singlet);

4.18 (2H, singlet);

4.83 (1H, doublet of doublets, J = 4 & 10Hz);

6.94 (2H, doublet, J = 9Hz);

7.25 (2H, doublet, J = 9Hz);

10.2 (1H, broad singlet, disappeared adding heavy water).

EXAMPLE 54

2-Methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-4-hydroxyimino-2,5,7,8-tetramethylchroman-6-yloxy}acetate

A mixture of 0.6 g of 2-methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethyl-4-oxochroman-6-yloxy}acetate (prepared as described in Example 35), 0.3 g of hydroxylamine hydrochloride, 0.3 g of pyridine and 6 ml of methanol was allowed to stand at 25-30°C for 2 days. Ethyl acetate and an aqueous solution of potassium carbonate were added to the mixture, and the organic layer was separated. The organic layer was dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was subjected to silica gel column chromatography (eluted with a 7:3 by volume mixture of benzene and ethyl acetate) to obtain the title compound.

Rf value on silica gel thin layer chromatography = 0.32 (tailing) (developing solvent, benzene:ethyl acetate = 3:2 by volume).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.43 (3H, singlet);

2.06 (3H, singlet);

2.20 (3H, singlet);

2.46 (3H, singlet);

2.8-3.55 (2H, nd);

3.10 (2H, AB type, J = 13.5Hz);

3.32 (3H, singlet);

3.55-3.7 (2H, multiplet);

4.08 (2H, AB type, J = 6Hz);

4.25-4.4 (2H, multiplet);

4.34 (2H, singlet);

4.76 (1H, double of doublets, J=4 & 9Hz);

6.93 (2H, doublet, J=9Hz);

7.24 (2H, doublet, J=9Hz);

10.0-10.6 (1H, broad, disappeared on adding heavy water).

EXAMPLE 55

t-Butyl α-{5-[4-(6-t-butoxycarbonylmethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate

A mixture of 0.5 g of t-butyl α-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate (prepared as described in Example 51), 0.2 g of hydroxylamine hydrochloride, 0.2 g of pyridine and 5 ml of methanol was allowed to stand at 25-30°C for 5 days. Ethyl acetate and an aqueous solution of potassium carbonate were added to the mixture, and the organic layer was separated. The organic layer was dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was subjected to silica gel column chromatography (eluted with a 20:1 by volume mixture of benzene and ethyl acetate) to obtain the title compound.

Rf value on silica gel thin layer chromatography = 0.43 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.45 (3H, singlet);

1.47 (9H, singlet);

1.54 (9H, singlet);

2.07 (3H, singlet);

2.23 (3H, singlet);

2.47 (3H, singlet);

2.85-3.15 (1H, nd);

3.08 (2H, singlet);

3.57 (1H, doublet of doublets, J=4 & 13.5Hz);

3.97 (2H, singlet);

4.20 (4H, singlet);

4.46 (1H, doublet of doublets, J=4 & 9Hz);

6.87 (2H, doublet, J=9Hz);

7.15 (2H, doublet, J=9Hz);

7.5-8.05 (1H, broad).

EXAMPLE 56

Di-t-butyl α,α'-{5-[4-(6-t-butoxycarbonylmethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetate

A mixture of 350 mg of di-t-butyl α,α'-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxo chroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetate (prepared as described in Example 50), 122 mg of hydroxylamine hydrochlorid , 122 mg of pyridine and 4 ml of methanol was allowed to stand at 25-30°C for 5 days. Ethyl acetate and an aqueous solution of potassium carbonate were added to the mixture, and the organic layer was separated. The organic layer was dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was subjected to silica gel column chromatography (eluted with a 20:1 by volume mixture of benzene and ethyl acetate) to obtain the title compound.

Rf value on silica gel thin layer chromatography = 0.48 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.45 (21H, singlet);

1.53 (9H, singlet);

2.08 (3H, singlet);

2.23 (3H, singlet);

2.47 (3H, singlet);

2.9-3.2 (2H, nd);

3.07 (2H, broad singlet);

3.22 (2H, singlet);

3.95 (2H, broad singlet);

4.11 (2H, singlet);

4.18 (2H, singlet);

6.83 (2H, doublet, J = 9Hz);

7.13 (2H, doublet, J = 9Hz);

7.68 (1H, broad singlet).

EXAMPLE 57

Ethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenoxymethyl]-4-hydroxyimino-2,5,7,8-tetramethylchroman-6-yloxy}acetate

Following the procedure described in Example 54, the title compound was obtained as a pale yellow powder by using 330 mg of ethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethyl-4-oxochroman-6-yloxy}acetate (prepared as described in Example 43), 170 mg of hydroxylamine hydrochloride, 170 mg of pyridine and 3 ml of methanol.

Rf value on silica gel thin layer chromatography = 0.67 (developing solvent, benzene:ethyl acetate = 1:1 by volume).

Mass spectrum (m/e): 556 (M^+).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.27 (3H, triplet, J = 7Hz);

1.43 (3H, singlet);

2.06 (3H, singlet);

2.20 (3H, singlet);

2.46 (3H, singlet);

2.95-3.25 (1H, nd);

3.08 (2H, singlet);

3.43 (1H, doublet of doublets, J = 4 & 14Hz);

4.08 (2H, singlet);

4.1-4.4 (2H, nd);

4.30 (2H, singlet);

4.74 (1H, doublet of doublets, J = 4 & 9Hz);

6.83 (2H, doublet, J = 9Hz);

7.23 (2H, doublet, J = 9Hz);

10.30 (1H, broad singlet, disappeared on adding heavy water).

EXAMPLE 58

α-{2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)-phenoxymethyl]-2,5,7,8-tetramethylchroman-6-yloxy}acetic acid

A mixture of 220 mg of 2-methoxyethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-2,5,7,8-tetramethylchroman-6-yloxy}acetate (prepared as described in Example 41), 3 ml of a 4N dioxane solution of hydrogen chloride and 0.3 ml of water was heated under reflux for 5 hours. At the end of this time, the solvent was distilled off and the residue was washed with water to give the title compound as a pale yellow powder.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm.

1.38 (3H, singlet);

1.8-2.2 (2H, nd);

2.02 (3H, singlet);

2.15 (6H, singlet);

2.65 (2H, broad triplet, J = 7Hz);

3.08 (1H, doublet of doublets, J = 9 & 14Hz);

3.41 (1H, doublet of doublets, J = 4 & 14Hz);

4.00 (2H, singlet);

4.27 (2H, singlet);

4.73 (1H, doublet of doublets, J = 4 & 9Hz);

6.92 (2H, doublet, J = 9Hz);

7.23 (2H, doublet, J = 9Hz);

9.9-11.3 (1H, broad, disappeared on adding heavy water).

Mass spectrum (m/): 499 (M^+).

EXAMPLE 59

α-{2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)-phenoxymethyl]-2,5,7,8-tetramethyl-4-oxochroman-6-yloxy}acetic acid

After eluting the 2-methoxyethyl ester which was obtained from the silica gel column chromatography described in Example 35, the title compound was obtained as pale yellow powder by continuing the elution with a 2:2:1 by volume mixture of ethyl acetate, tetrahydrofuran and methanol.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm

1.41 (3H, singlet);

2.02 (3H, singlet);

2.18 (3H, singlet);

2.46 (3H, singlet);

2.68 (1H, doublet, J=16Hz);

2.85-3.20 (2H, nd);

3.22 (1H, doublet of doublets, J=4 & 14Hz);

4.01 (2H, singlet);

4.12 (2H, singlet);

4.61 (1H, doublet of doublets, J=4 & 9Hz);

6.87 (2H, doublet, J=9Hz);

7.15 (2H, doublet, J=9Hz).

Mass spectrum (m/e): 513 (M^+).

EXAMPLE 60

α-{2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)-phenoxymethyl]-4-hydroxyimino-2,5,7,8-tetramethylchroman-6-yloxy}acetic acid

A mixture of 8.9 mg of ethyl α-{2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxymethyl]-4-hydroxyimino-2,5,7,8-tetramethylchroman-6-yloxy}acetate [prepared as described in Example 57], 1 ml of ethanol and 0.2 ml of a 0.312 M aqueous solution of sodium hydroxide was allowed to stand for 19 hours at 0-5°C.

After the absence of the starting material had been confirmed by high pressure liquid chromatography, 0.56 ml of 0.35% w/v aqueous hydrochloric acid was then added to the reaction mixture. The solvent was distilled off under reduced pressure, and chloroform and water were added to the residue.

The pale yellow precipitate was filtered and then washed with water, to give the title compound.

Fast Atom Bombardment Mass Spectrum (m/ measured with glycerol as a matrix):

$[M+H]^+$ = 529.

$[M-H]^-$ = 527.

From the above data, the molecular weight was deduced to be 528.

EXAMPLE 61

α-{5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid

A mixture of 1.0 g of t-butyl α-{5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate (prepared as described in example 46) and 10 ml of a 4N dioxane solution of hydrogen chloride was allowed to stand at room temperature overnight. At the end of this time, the solvent was distilled off and the residue was washed with water to give the title compound as a pale yellow powder, softening at 85-90°C.

Nuclear Magnetic Resonance Spectrum: the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

Mass spectrum (m/e): 499 (M^+).

EXAMPLE 62

α-{5-[4-(6-Hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid

A mixture of 350 mg of t-butyl α-{5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2, 4-dioxothiazolidin-3-yl}acetate (prepared as described in Example 49) and 4 ml of a 4N dioxane solution of hydrogen chloride was treated in the same manner described in Example 61, to give the title compound as a pale yellow powder, softening at 60-70°C.

Nuclear Magnetic Resonance Spectrum: the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

Mass spectrum (m/e): 513 (M^+).

EXAMPLE 63

α-{5-[4-(6-Hydroxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid

A mixture of 400 mg of 5-butyl α-{5-[4-(6-hydroxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate (prepared as described in Example 53) and 5 ml of a 4N dioxane solution of hydrogen chloride was treated in the same manner described in Example 61, to give the title compound as a pale brown powder, softening at 90-95°C.

Nuclear Magnetic Resonance Spectrum: the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

EXAMPLE 64

α-{5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid

A mixture of 0.63 g of t-butyl α-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate (prepared as described in Example 48) and 6 ml of a 4N dioxane solution of hydrogen chloride was allowed to stand at room temperature overnight. At the end of this time, the reaction mixture was treated as the same manner described in Example 61, to give the title compound as a pale yellow powder, softening at 95-100°C.

Nuclear Magnetic Resonance Spectrum: the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

Mass spectrum (m/e): 557 (M^+).

EXAMPLE 65

α-{5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid

A mixture of 570 mg of t-butyl α-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetate (prepared as described in Example 51) and 6 ml of a 4N dioxane solution of hydrogen chloride was treated in the same manner described in Example 61, to give the title compound as a pale yellow powder, softening at 80-85°C.

Nuclear Magnetic Resonance Spectrum: the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

Mass spectrum (m/e): 571 (M^+).

EXAMPLE 66

α-{5-[4-(6-Carboxymethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid

A mixture of 370mg of t-butyl α-{5-[4-(6-t-butoxycarbonylmethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2, 4-dioxothiazolidin-3-yl}acetate (prepared as described in Example 55) and 4 ml of a 4N dioxane solution of hydrogen chloride was treated in the same manner described in Example 61, to give the title compound as a pale yellow powder, softening at 90-100°C.

Nuclear Magnetic Resonance Spectrum : the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

EXAMPLE 67

α,α'-{5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetic acid

A mixture of 0.41g of di-t-butyl α,α'-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetate (prepared as described in Example 47) and 4 ml of a 4N dioxane solution of hydrogen chloride was allowed to stand at room temperature overnight. At the end of this time, the reaction mixture was treated in the same manner described in Example 61, to give the title compound as a pale yellow powder, softening at 105 -110°C.

Nuclear Magnetic Resonance Spectrum : the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

Mass Spectrum (m/e): 615 (M^+).

EXAMPLE 68

α,α'-{5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetic acid

A mixture of 340 mg of di-t-butyl α,α'-{5-[4-(6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetate (prepared as described in Example 50) and 4 ml of a 4N dioxane solution of hydrogen chloride was treated in the same manner described in Example 61, to give the title compound as a pale yellow powder, softening at 105-110°C.

Nuclear Magnetic Resonance Spectrum : the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

Mass Spectrum (m/e): 629 (M^+).

EXAMPLE 69

α,α'-{5-[4-(6-Carboxymethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetic acid

A mixture of 270 mg of di-t-butyl α,α'-{5-[4-(6-t-butoxycarbonylmethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetate (prepared as described in Example 56) and 3 ml of a 4N dioxane solution of hydrogen chloride was treated in the same manner described in Example 61, to give th title compound as a pale yellow powder, softening at 90-100°C.

Nuclear Magnetic Resonance Spectrum: the signal assigned to the t-butyl group had disappeared, as compared with the spectrum of the starting material.

EXAMPLE 70

5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione sulphuric acid ester

A solution of 5 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (synthesized as described in copending EP-A 0139421) in 10 ml of pyridine was added to a solution of 7.3 g (62.64 mmole) of chlorosulphonic acid in 20 ml of pyridine, and the reaction mixture was heated at 70-80°C for 1 hour. At the end of this time, petroleum ether was added to the reaction mixture, the supernatant liquid was removed by decantation, and then these procedures were repeated a further 2 times. 10 ml of water were added to the resulting residue. The reaction mixture was adjusted to a pH value of 6.5 with a 2N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate was distilled from the extract under reduced pressure, to give 5.72 g of the title compound as a white powder, melting at 140.5-142.5°C.

Infrared Absorption Spectrum (Nujol-trade mark-mull): $\nu_{max}cm^{-1}$:

3600, 3330, 1270, 1050.

Nuclear Magnetic Resonance Spectrum: (CD_3CN) δ ppm:

7.2 (2H, doublet);

6.9 (2H, doublet);

4.8 (1H, doublet of doublets);

4.0 (1H, doublet);

3.9 (1H, doublet);

3.3 (1H, doublet of doublets);

3.1 (1H, doublet of doublets);

2.6 (2H, triplet);

2.19 (3H, singlet);

2.18 (3H, singlet);

2.1 (1H, multiplet);

2.0 (3H, singlet);

1.9 (1H, multiplet);

1.4 (3H, singlet).

Fast Atom Bombardment Mass Spectrum (m/e measured with glycerol as a matrix):

$(M+H)^+ = 522$;

$(M-H)^- = 520$.

From this, we concluded that molecular weight is 521.

PREPARATION 1

Ethyl 6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-carboxylate (Step E1)

12 g of ethyl 6-hydroxy-5,7,8-trimethyl-4-oxo-2H-chromene-2-carboxylate [prepared as described in J. Med. Chem., 18 , 934 (1975)] were dissolved in 250 ml of dimethylformamide and reduced catalytically in the presence of 16 g of 10% w/w palladium-on-carbon, under a hydrogen pressure of 5 atmospheres at 50 to 60°C for 7 hours. The catalyst was then filtered off, and the filtrate was mixed with a large amount of water. The crystals which separated were collected by filtration and then recrystallized from ethyl acetate, to give the title compound, melting at 120-121°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.26 (3H, triplet, J=7Hz);

2.23 (6H, singlet);

2.52 (3H, singlet);

2.98 (2H, doublet J=7Hz);

4.24 (2H, quartet, J=7Hz);

4.83 (1H, singlet);

4.94 (1H, triplet, J=7Hz).

The filtrate from which the title compound had been filtered off was extracted with ethyl acetate. The solution was dried over anhydrous sodium sulphate, and the solvent was distilled off. The residue was purified by silica gel column chromatography, eluted with a 1:1 by volume mixture of hexane and ethyl acetate. The first fraction gave the title compound, while the second fraction gave ethyl 4,6-dihydroxy-5,7,8-trimethyl-chroman-2-carboxylate, melting at 138-144°C.

PREPARATION 2

Ethyl 6-hydroxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane)-2-carboxylate (Step E2)

20 ml of a boron trifluoride-acetic acid complex salt (boron trifluoride content 40% w/w) were added dropwise to 500 ml of a chloroform solution containing 18.6 g of ethyl 6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-carboxylate (prepared as described in Preparation 1) and 9.7 g of 1,3-propanedithiol in an ice bath, and the reaction mixture was allowed to stand for 24 hours at room temperature. The reaction mixture was then poured into ice-water, neutralized with potassium carbonate and extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulphate and the solvent was distilled off. Recrystallization of the residue from ethyl acetate afforded the title compound, melting at 186-188°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.35 (3H, triplet, J=7Hz);

1.8-2.4 (2H, nd);

2.18 (6H, singlet);

2.5-2.9 (3H, nd);

2.80 (3H, singlet);

3.0-3.5 (3H, multiplet);

4.31 (2H, quartet, J=7Hz);

4.50 (1H, singlet);

4.79 (1H, doublet of doublets, J=2 & 10Hz).

PREPARATION 3

Ethyl 6-methoxymethoxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithian)-2-carboxylate (Step E3)

A mixture of 6.6 g of ethyl 6-hydroxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane)-2-carboxylate (prepared as described in Preparation 2), 100 ml of dimethylformamide and 1 g of a 55% w/w suspension of sodium hydride in mineral oil was subjected to ultrasonic treatment for mixing at room temperature for 1 hour, and then, whilst ice-cooling, 3 g of chloromethyl methyl ether were added, and the mixture was allowed to stand at room temperature overnight. water was added to the reaction mixture, which was then extracted with ethyl acetate. The water layer was extracted additionally with benzene. Both the ethyl acetate and benzene extracts were washed with water three times, after which the extracts were combined and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography, eluted with a 5:1 by volume mixture of hexane and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.21 (developing solvent, hexane:ethyl acetate = 5:1 by volume).

Nuclear Magnet Resonance Spectrum ($CDCl_3$) δ ppm:

1.34 (3H, triplet, J = 7Hz);

1.72-2.4 (2H, nd);

2.16 (3H, singlet);

2.21 (3H, singlet);

2.5-3.0 (3H, nd);

2.87 (3H, singlet);

3.0-3.5 (3H, nd);

3.60 (3H, singlet);

4.30 (2H, quartet, J = 7Hz);

4.7-5.0 (1H, nd);

4.89 (2H, singlet).

PREPARATION 4

2-Hydroxymethyl-2-isobutyl-6-methoxymethoxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane) (Steps E4 & E5)

15 ml of a hexane solution of butyllithium (butyllithium content 1.62 mmole/ml) were added dropwise at a temperature of -60°C to -50°C to 90 ml of a tetrahydrofuran solution containing 3 g of diisopropylamine, and the mixture was allowed to stand for 20 minutes at room temperature. 4.8 g of ethyl 6-methoxymethoxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane)-2-carboxylate (prepared as described in Preparation 3) were added at -60°C to the mixture, which was then stirred for 10 minutes at the same temperature. 4.1 g of isobutyl bromide were added, and the mixture was stirred for 30 minutes at the same temperature, and then stirred at room temperature for 1.5 hours. Another 3 g of isobutyl bromide were added, and the mixture was heated at 40°C for 5 hours. The reaction mixture was then cooled to -50°C, 0.6 g of lithium aluminium hydride were added, and the mixture was stirred for 1 hour at room temperature. Benzene, ethyl acetate and water were added to this reaction mixture. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography, eluted with a 5:1 by volume mixture of hexane and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.16 (developing solvent, hexane:ethyl acetate = 5:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.03 (3H, doublet, J = 6Hz);

1.04 (3H, doublet, J = 6Hz);

1.70 (2H, doublet, J = 6Hz);

1.8-2.3 (3H, nd);

2.08 (3H, singlet);

2.20 (3H, singlet);

2.3-3.0 (4H, nd);

2.91 (3H, singlet);

3.05-3.95 (5H, nd);

3.82 (3H, singlet);

4.88 (2H, singlet).

PREPARATION 5

2-Isobutyl-6-methoxymethoxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chromanspiro-4,2'-(1',3'-dithiane) (Step E6)

4 ml of ethanol were added to a mixture of 0.6 g of a 55% w/w suspension of sodium hydride in mineral oil and 20 ml of tetrahydrofuran, followed by 20 ml of a tetrahydrofuran solution containing 3.2 g of 2-hydroxymethyl-2-isobutyl-6-methoxymethoxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane) (prepared as described in Preparation 4). The solvent was then distilled off under reduced pressure to dryness. The residue was mixed with 30 ml of dimethylformamide and heated at 40°C for 1 hour under reduced pressure. 10 g of p-nitrochlorobenzene were then added to the reaction mixture, and the mixture was heated at 50°C for 2 hours, mixed with water and extracted with benzene. The benzene extract was washed twice with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography eluted with a 6:1 by volume mixture of hexane and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.54 (developing solvent, hexane:ethyl acetate = 2:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.02 (3H, doublet, J = 6HZ);

1.09 (3H, doublet, J = 6Hz);

1.83 (2H, doublet, J = 6Hz);

1.8-2.3 (3H, nd);

2.11 (3H, singlet);

2.22 (3H, singlet);

2.3-2.9 (3H, nd);

2.89 (3H, singlet);

3.0-3.7 (3H, nd);

3.62 (3H, singlet);

3.92 (1H, doublet, J = 4.5Hz);

4.50 (1H, doublet, J = 4.5Hz);

4.90 (2H, singlet);

6.90 (2H, doublet, J = 4.5Hz);

8.17 (2H, doublet, J = 4.5Hz).

PREPARATION 6

(a) 2-Isobutyl-6-methoxymethoxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one and (b) 6-hdyroxy-2-isobutyl-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one (Step E7)

A mixture of 3.3 g of 2-isobutyl-6-methoxymethoxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chromanspiro-4,2'-(1',3'-dithiane) (prepared as described in Preparation 5), 4 g of mercuric chloride, 1.4 g of mercuric oxide and 30 ml of 10% v/v aqueous methanol was heated under reflux for 2 hours. The reaction mixture was then mixed with diethyl ether, and the insoluble residue was filtered off. The filtrate was washed with an aqueous solution of sodium chloride and then with an aqueous solution of ammonium sulphate, and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was purified by silica gel column chromatography eluted with a 4:1 by volume mixture of hexane and ethyl acetate, to give the title compounds (a) and (b) separately.

Silica gel thin layer chromatography - (developing solvent, hexane:ethyl acetate = 2:1 by volume).

(a) Rf value = 0.48

(b) Rf value = 0.40.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

(a) 1.01 (6H, doublet, J = 6Hz);

1.84 (2H, singlet);

1.6-2.1 (1H, nd);

2.12 (3H, singlet);

2.27 (3H, singlet);

2.58 (3H, singlet);

2.81 (1H, doublet, J=19Hz);

3.00 (1H, doublet, J=19Hz);

3.62 (3H, singlet);

4.14 (1H, doublet, J=11Hz);

4.25 (1H, doublet, J=11Hz);

4.89 (2H, singlet);

6.95 (2H, doublet, J=4.5Hz);

8.20 (2H, doublet, J=4.5Hz).

(b) 0.98 (3H, doublet, J=6Hz);

1.00 (3H, doublet, J=6Hz);

1.80 (2H, doublet, J=6Hz);

1.65-2.1 (1H, nd);

2.13 (3H, singlet);

2.23 (3H, singlet);

2.57 (3H, singlet);

2.82 (1H, doublet, J=14Hz);

3.00 (1H, doublet, J=14Hz);

4.13 (1H, doublet, J=12Hz);

4.27 (1H, doublet, J=12Hz);

4.66 (1H, singlet);

6.95 (2H, doublet, J=9Hz);

8.19 (2H, doublet, J=9Hz).

PREPARATION 7

6-Acetoxy-2-isobutyl-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one

A mixture of 1.5 g of 6-hydroxy-2-isobutyl-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 6) and 30 ml of pyridin was mixed with 3 g of acetic anhydride and stirred for 35 hours at room temperatur . Th reaction mixture was then condensed by evaporation under reduced pressure, mixed with water and extracted with ethyl acetate and benzene. The extract was dried over anhydrous sodium sulphate, and the solvent was distilled off under reduced pressure. The r sidue was purified by silica gel column chromatography, using a 5:1 by volume mixture of hexane and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatogrraphy = 0.42 (developing solvent, hexane:ethyl acetate = 2:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.01 (6H, doublet, J=6Hz);

1.7-2.2 (3H, nd);

2.09 (3H, singlet);

2.12 (3H, singlet);

2.33 (3H, singlet);

2.42 (3H, singlet);

2.91 (2H, AB type, J=18Hz);

4.13 & 4.25 (2H, AB type, J=9Hz);

6.95 (2H, doublet, J=9Hz);

8.20 (2H, doublet, J=9Hz).

PREPARATION 8

6-Acetoxy-2-(4-aminophenoxymethyl)-2-isobutyl-5,7,8-trimethylchroman-4-one

1.4g of 6-acetoxy-2-isobutyl-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 7) was dissolved in 35 ml of methanol, and, in the presence of 1 g of 10% w/w palladium-on-carbon, it was reduced for 3 hours under about 1 atmosphere (about 1 bar) pressure of hydrogen. The catalyst was filtered off, and the solvent was then distilled off under reduced pressure to give the title compound.

Rf value on silica gel thin layer chromatography = 0.54 (developing solvent, ethyl acetate).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.97 (6H, doublet, J = 6Hz);

1.6-2.2 (3H, nd);

2.08 (3H, singlet);

2.14 (3H, singlet);

2.32 (3H, singlet);

2.42 (3H, singlet);

2.74 & 3.02 (2H, AB type, J = 16Hz);

3.2-3.7 (2H, broad singlet);

3.94 & 4.06 (2H, AB type, J = 9Hz);

6.58 (2H doublet, J = 9Hz);

6.73 (2H, doublet, J = 9Hz).

PREPARATION 9

Ethyl 3-[4-(6-acetoxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate (Step D3)

1.5 ml of concentrated hydrochloric acid was added to mixture of 1.1 g of 6-acetoxy-2-(4-aminophenoxy-methyl)-2-isobutyl-5,7,8,-trimethylchroman-4-one (prepared as described in Preparation 8) and 20 ml of acetone under a nitrogen stream and at room temperature. This was followed by 0.8 g of sodium nitrite and 0.3 ml of water, and then by 4 g of ethyl acrylate. 0.1 g of cuprous oxide was added at room temperature to the reaction mixture, which was then stirred for 1 hour. Water was then added, and the mixture was extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulphate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography using a 5.1 by volume mixture of hexane and ethyl acetate as eluent, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.74 (developing solvent, hexane:ethyl acetate = 1:2 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.98 (6H, doublet, J = 6Hz);

1.25 (3H, triplet, J = 7Hz);

1.5-2.2 (3H, nd);

2.08 (3H, singlet);

2.13 (3H, singlet);

2.32 (3H, singlet);

2.42 (3H, singlet);

2.78 & 3.01 (2H, AB type, J = 17Hz);

2.8-3.5 (2H, nd);

3.8-4.5 (5H, nd);

6.82 (2H, doublet, J = 9Hz);

7.11 (2H, doublet, J = 9Hz).

PREPARATION 10

Ethyl 6-hydroxy-5,7,8-trimethylchroman-2-carboxylate (Step C4)

14 g of ethyl 6-hydroxy-5,7,8-trimethyl-4-oxo-2H-chromene-2-carboxylate [prepared as described in J. Med. Chem. 18, 934 (1975)] were dissolved in 320 ml of acetic acid, and the resulting solution was catalytically reduced for 1 hour at 60-65°C, under a hydrogen pressure of 3 atmospheres and in the presence of 3.5 g of 10% w/w palladium-on-carbon. The catalyst was filtered off, and the filtrate was poured into water. The white crystals which separated were collected by filtration, to give the title compound, melting at 108-109°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.28 (3H, triplet, J = 7Hz);

2.07 (3H, singlet);

2.17 (6H, singlet);

1.9-2.3 (2H, nd);

2.65 (2H, broad triplet, J = 7Hz);

4.22 (2H, quartet, J=7Hz);

4.1-4.3 (1H, nd);

4.60 (1H, doublet of doublets, J=7 & 4Hz).

PREPARATION 11

Ethyl 6-methoxymethoxy-5,7,8-trimethylchroman-2-carboxylate (Step C5)

3 g of a 55% w/w suspension of sodium hydride in mineral oil were washed twice with cyclohexane. A mixture of 14.3 g of ethyl 6-hydroxy-5,7,8-trimethyl-chroman-2-carboxylate (prepared as described in Preparation 10) and 130 ml of dimethylformamide was added slowly to this suspension under a nitrogen stream at 5-10°C. The reaction mixture was stirred for 1 hour, and then cooled in ice to 3-5°C, after which 5.6 g of chloromethyl methyl ether were added dropwise. After this addition, the reaction mixture was stirred for 1 hour at room temperature, poured into ice-water, and then extracted with cyclohexane. The cyclohexane extract was washed with water and dried over anhydrous sodium sulphate. The solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography using a 25:1 by volume mixture of benzene and ethyl acetate as eluent, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.41 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.27 (3H, triplet, J=7Hz);

2.0-2.4 (2H, nd);

2.15 (3H, singlet);

2.16 (3H, singlet);

2.2 (3H, singlet);

2.64 (2H, broad triplet, J=7Hz);

3.61 (3H, singlet);

4.24 (2H, quartet, J=7Hz);

4.64 (1H, doublet of doublets, J=4 & 7Hz);

4.87 (2H, singlet).

PREPARATION 12

Ethyl 6-methoxymethoxy-5,7,8-trimethyl-2-octylchroman-2-carboxylate (Step C6)

7.8 ml of a hexane solution containing 1.62 mmole/ml of butyllithium were added dropwise to a mixture of 2 g of diisopropylamine and 80 ml of tetrahydrofuran under a nitrogen stream at a temperature from -60 to -50°C. The resulting mixture was then allowed to stand for 10 minutes at room temperature, after which about 10 ml of tetrahydrofuran containing 4 g of ethyl 6-methoxymethoxy-5,7,8-trimethylchroman-2-carboxylate (prepared as described in Preparation 11) were added and the mixture was stirred for 1 hour at -60°C. About 20 ml of tetrahydrofuran containing 5 g of octyl bromide were added, and the mixture was stirred for 1 hour at -60°C and then for 1 hour at room temperature, after which it was heated for 1 hour at 50°C. The reaction mixture was then poured into ice-water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure, and the residue was subjected to silica gel column chromatography eluted with benzene, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.58 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.89 (3H, broad triplet, J=6Hz);

1.15 (3H, triplet, J=7Hz);

1.2-1.6 (12H, multiplet);

1.6-2.4 (4H, multiplet);

2.1 (3H, singlet);

2.18 (3H, singlet);

2.2 (3H, singlet);

2.4-2.7 (2H, multiplet);

3.59 (3H, singlet);

4.11 (2H, quartet, J=7Hz);

4.85 (2H, singlet).

PREPARATION 13

6-Methoxymethoxy-5,7,8-trimethyl-2-octylchroman-2-ylmethanol (Step A1')

10 ml of tetrahydrofuran containing 3.3 g of ethyl 6-methoxymethoxy-5,7,8-trimethyl-2-octylchroman-2-carboxylate (prepared as described in Preparation 12) were added dropwise to a mixture of 0.45 g of lithium aluminium hydride and 30 ml of tetrahydrofuran under a nitrogen stream, and whilst ice-cooling. The resulting mixture was stirred for 3 hours at room temperature. Ethyl acetate and 5% w/v aqueous hydrochloric acid were then added to the reaction mixture, whilst ice-cooling, and the organic layer was separated. Then the aqueous layer was extracted with ethyl acetate. The organic layer and the extract were combined, washed with a saturated aqueous solution of sodium chloride and dried over anyhdrous sodium sulphate. The solvent was removed by distillation under reduced pressure, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.45 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.7-1.0 (3H, multiplet);

1.0-2.3 (16H, multiplet);

2.10 (3H, singlet);

2.15 (3H, singlet);

2.20 (3H, singlet);

2.59 (2H, broad triplet, J = 7Hz);

3.6 (5H, singlet);

4.87 (2H, singlet).

PREPARATION 14

6-Methoxymethoxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)-2-octylchroman (Step A2)

0.38 g of a 55% w/w suspension of sodium hydride in mineral oil was added to a mixture of 3 g of 6-methoxymethoxy-5,7,8-trimethyl-2-octylchroman-2-ylmethanol (prepared as described in Preparation 13) and 25 ml of dimethylformamide under a nitrogen stream at room temperature, and the resulting mixture was heated for 2 hours at 50°C. A mixture of 1.4 g of p-chloronitrobenzene and 2 ml of benzene was then added dropwise, whilst ice-cooling, and the resulting mixture was heated for 2 hours at 50°C. The reaction mixture was then poured into ice-water and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography eluted with benzene, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.46 (developing solvent, benzene).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.7-1.0 (3H, multiplet);

1.0-1.9 (14H, multiplet);

1.9-2.3 (2H, nd);

2.06 (3H, singlet);

2.15 (3H, singlet);

2.19 (3H, singlet);

2.6 (2H, broad triplet, J = 7Hz);

3.60 (3H, singlet);

4.05 (2H, singlet);

4.87 (2H, singlet);

6.97 (2H, doublet, J = 9Hz);

8.18 (2H, doublet, J = 9Hz).

PREPARATION 15

6-Hydroxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)-2-octylchroman (Step A3, Deprotection)

A mixture of 3.7 g of 6-methoxymethoxy 5,7,8-trimethyl-2-(4-nitrophenoxymethyl)-2-octylchroman (prepared as described in Preparation 14), 10 ml of acetic acid, 30 ml of benzene and 0.75 ml of 10% w/v aqueous sulphuric acid was heated under reflux for 30 minutes. The reaction mixture was then poured into water and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was re-

moved by distillation under reduced pressure, to give the title compound.

Rf value on silica gel thin lay r chromatography = 0.34 (developing solvent, benzene).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.7-1.0 (3H, multiplet);

1.0-1.85 (14H, multiplet);

1.85-2.2 (2H, nd);

2.10 (6H, singlet);

2.16 (3H, singlet);

2.63 (2H, broad triplet, J = 7Hz);

4.06 (2H, singlet);

4.19 (1H, singlet, disappeared on adding heavy water);

6.97 (2H, doublet, J = 9Hz);

8.19 (2H, doublet, J = 9Hz).

PREPARATION 16

6-Acetoxy-5, 7, 8-trimethyl-2-(4-nitrophenoxymethyl)-2-octylchroman (Step A3, Acylation)

1.2 g of acetic anhydride was added to a mixture of 3.5 g of 6-hydroxy-5, 7, 8-trimethyl-2-(4-nitrophenoxymethyl)-2-octylchroman (prepared as described in Preparation 15), 10 ml of pyridine and 10 ml of benzene, and the mixture was stirred for 2 hours at room temperature. The reaction mixture was then poured into water and extracted with benzene. The extract was washed with 5% w/v aqueous hydrochloric acid and water, successively in that order, and dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.4 (developing solvent, benzene).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.75-1.0 (3H, multiplet);

1.1-1.65 (12H, multiplet);

1.65-2.15 (4H, nd);

1.99 (3H, singlet);

2.04 (3H, singlet);

2.08 (3H, singlet);

2.32 (3H, singlet);

2.63 (2H, broad triplet, J = 7Hz);

4.07 (2H, singlet);

6.98 (2H, doublet, J = 9Hz);

8.20 (2H, doublet, J = 9Hz).

PREPARATION 17

6-Acetoxy-2-(4-aminophenoxymethyl)-5,7,8-trimethyl-2-octylchroman (Step A3, Hydrogenation)

Using Paar's hydrogenation apparatus, a mixture of 4 g of 6-acetoxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)-2-octylchroman (prepared as described in Preparation 16), 0.8 g of 10% w/w palladium-on-carbon, 30 ml of methanol and 10 ml of benzene was stirred for 5 hours under 3-5 atmospheres (about 3-5 bars) pressure of hydrogen. The catalyst was filtered off, and the filtrate was condensed by evaporation under reduced pressure. The crystals thus obtained were washed with hexane to give the title compound, melting at 112-114°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.7-1.05 (3H, multiplet);

1.05-1.65 (12H, multiplet);

1.65-2.2 (4H, nd);

1.97 (3H, singlet);

2.02 (3H, singlet);

2.10 (3H, singlet);

2.31 (3H, singlet);

2.59 (2H, broad triplet, J = 7Hz);

3.0-3.7 (2H, broad singlet, disappeared on adding heavy water);

3.86 (2H, singlet);

6.62 (2H, doublet, J = 10Hz);

6.75 (2H, doublet, J = 10Hz).

PREPARATION 18

Ethyl 3-[4-(6-acetoxy-5,7,8-trimethyl-2-octylchroman-2-ylmethoxy)phenyl]-2-chloropropionate (Step A4)

3.5 ml of concentrated hydrochloric acid, 1.7 ml of water containing 0.61 g of sodium nitrate and 7.2 ml of ethyl acrylate were added dropwise successively, in that order, under a nitrogen stream and at 5-10°C, to a mixture of 3.2 g of 6-acetoxy-2-(4-aminophenoxy methyl)-5, 7, 8-trimethyl-2-octylchroman (prepared as described in Preparation 17) and 35 ml of acetone. The reaction mixture was then heated to 40-43°C (inner temperature), and 0.1 g of cuprous oxide was slowly added. After about 30 minutes, nitrogen generation ceased. The reaction mixture was then poured into water and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography using a 10:1 by volume mixture of cyclohexane and ethyl acetate as eluent, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.27 (developing solvent, cyclohexane:ethyl acetate = 9:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.8-1.05 (3H, multiplet);

1.05-1.65 (15H, multiplet);

1.65-2.2 (4H, nd);

1.97 (3H, singlet);

2.03 (3H, singlet);

2.09 (3H, singlet);

2.30 (3H, singlet);

2.6 (2H, broad triplet, J = 7Hz);

3.07 (1H, doublet of doublets, J = 7 & 14Hz);

3.30 (1H, doublet of doublets, J = 7 & 14Hz);

3.92 (2H, singlet);

4.18 (2H, quartet, J = 7Hz);

4.36 (1H, triplet, J = 7Hz);

6.85 (2H, doublet, J = 9Hz);

7.13 (2H, doublet, J = 9Hz).

PREPARATION 19

6-Acetoxy-2-methyl-2-(4-nitrophenoxymethyl-7-(1,1,3,3-tetramethylbutyl)chroman-4-one (Step D1)

A mixture of 23 g of 5-acetoxy-2-hydroxy-4-(1,1,3,3-tetramethylbutyl)acetophenone, 14.7 g of 1-(4-nitrophenoxy)-2-propanone, 8 g of pyrrolidine and 300 ml of benzene was stirred for 3 hours at room temperature, and then heated under reflux for 10 hours. The reaction mixture was then poured into ice-water and extracted with benzene. The extract was washed with 5% w/v aqueous hydrochloric acid and water successively in that order, and then dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure. The residue was mixed with 15 g of acetic anhydride and 400 ml of pyridine, and the mixture was allowed to stand for 1 day at room temperature. The reaction mixture was then poured into ice-water and extracted with benzene. The extract was washed with 5% w/v aqueous hydrochloric acid and water in that order, and then dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography, eluted with a 20:1 by volume mixture of benzene and ethyl acetate, and recrystallized from methanol, to give the title compound melting at 165.5-167°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.76 (9H, singlet);

1.36 (6H, singlet);

1.57 (3H, singlet);

1.83 (2H, singlet);

2.32 (3H, singlet);

2.74 (1H, doublet, J = 17Hz);

3.10 (1H, doublet, J = 17Hz);

4.11 & 4.24 (2H, AB type, J = 9Hz);

6.95 (2H, doublet J = 9Hz);

6.98 (1H, singlet);

7.50 (1H, singlet);

8.20 (2H, doublet, J = 9Hz).

PREPARATION 20

6-Acetoxy-4-hydroxy-2-methyl-2-(4-nitrophenoxymethyl)-7-(1,1,3,3-tetramethylbutyl)-chroman (Step F1)

1g of sodium borohydride was added, whilst ice-cooling, to a mixture of 100 ml of methanol and 10 ml of benzene containing 13 g of 6-acetoxy-2-methyl-2-(4-nitrophenoxymethyl)-7-(1,1,3,3-tetramethylbutyl)chroman-4-one (prepared as described in Preparation 19), and the mixture was stirred for 30 minutes whilst ice-cooling. The reaction mixture was then poured into ice-water, neutralized with 10% w/v aqueous hydrochloric acid and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography, eluted with a 4:1 by volume mixture of benzene and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.32 (developing solvent, benzene:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.77 (9H, singlet);

1.34 (6H, singlet);

1.54 (3H, singlet);

1.80 (2H, singlet);

1.85-2.25 (1H, nd);

2.29 (3H, singlet);

2.48 (1H, doublet of doublets, J = 7 & 14Hz);

4.02 (2H, AB type, J = 12Hz);

4.7-5.0 (1H, multiplet);

6.85 (1H, singlet);

6.95 (2H, doublet, J = 9Hz);

7.08 (1H, singlet);

8.18 (2H, doublet, J = 9Hz).

PREPARATION 21

(a) 6-Hydroxy-2-methyl-2-(4-nitrophenoxymethyl)-7-(1,1,3,3-tetramethylbutyl)-2H-chromene and

(b) 6-Acetoxy-2-methyl-2-(4-nitrophenoxymethyl)-7-(1,1,3,3-tetramethylbutyl)-2H-chromene (Step F3)

A solution of 10.2 g of 6-acetoxy-4-hydroxy-2-methyl-2-(4-nitrophenoxymethyl)-7-(1,1,3,3-tetramethylbutyl)chroman (prepared as described in Preparation 20) and 0.4 g of p-toluenesulphonic acid in 200 ml of benzene was heated under reflux for 30 minutes under a nitrogen stream. The reaction mixture was then poured into ice-water and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography, eluted with benzene, to give the title compounds (a) and (b).

Rf value on silica gel thin layer chromatography (developing solvent, benzene:ethyl acetate = 20:1 by volume) = 0.53 and 0.50, respectively.

Nuclear Magnetic Resonance Spectrum (a) - ($CDCl_3$) δ ppm:

0.75 (9H, singlet);

1.38 (6H, singlet);

1.56 (3H, singlet);

1.89 (2H, singlet);

4.09 (2H, singlet);

4.43 (1H, singlet, disappeared on adding heavy water);

5.63 (1H, doublet, J = 10Hz);

6.32 (1H, singlet);

6.41 (1H, doublet, J = 10Hz);

6.73 (1H, singlet);

6.96 (2H, doublet, J = 9Hz);

8.20 (2H, doublet, J = 9Hz).

Nuclear Magnetic Resonance Spectrum (b) - ($CDCl_3$) δ ppm:

0.76 (9H, singlet);

1.32 (6H, singlet);

1.58 (3H, singlet);

1.79 (2H, singlet);

2.29 (3H, singlet);

4.10 (2H, singlet);

5.62 (1H, doublet, J = 10Hz);

6.43 (1H, doublet, J = 10Hz);

6.69 (1H, singlet);

6.79 (1H, singlet);

6.93 (2H, doublet, J = 9Hz);

8.18 (2H, doublet, J = 9Hz).

PREPARATION 22

6-Acetoxy-2-(4-aminophenoxymethyl)-2-methyl-7-(1,1,3,3-tetramethylbutyl)chroman (Step F5)

Using Paar's hydrogenation apparatus, a mixture of 9.1 g of 6-acetoxy-2-methyl-2-(4-nitrophenoxymethyl)-7-(1,1,3,3-tetramethylbutyl)-2H-chromene (prepared as described in Preparation 21), 2 g of 10% w/w palladium-on-carbon and 150 ml of methanol was stirred for 10 hours under 3-5 atmospheres (about 3-5 bars) pressure of hydrogen. The catalyst was filtered off, and the filtrate was condensed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography, luted with a 10:1 by volum mixture of benzene and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.27 (developing solvent, benzene:ethyl acetate = 9:1 by volum).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.77 (9H, singlet);

1.34 (6H, singlet);

1.42 (3H, singlet);

1.7-2.2 (2H, nd);

1.78 (2H, singlet);

2.27 (3H, singlet);

2.65 (2H, broad quartet, J = 7Hz);

3.36 (2H, broad singlet, disappeared on adding heavy water);

3.85 (2H, AB type J = 9Hz);

6.54-6.88 (6H, multiplet).

PREPARATION 23

Ethyl 3-{4-[6-acetoxy-2-methyl-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]phenyl}-2-chloropropionate (Step A4)

Following the same procedure as described in Preparation 18, 7.9 g of 6-acetoxy-2-(4-aminophenoxymethyl)-2-methyl-7-(1,1,3,3-tetramethylbutyl)chroman (prepared as described in Preparation 22), 1.6 g of sodium nitrite, 9 ml of concentrated hydrochloric acid, 18 g of ethyl acrylate, 260 mg of cuprous oxide, 90 ml of acetone and about 5 ml of water were reacted, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.55 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.78 (9H, singlet);

1.22 (3H, triplet, J = 7Hz);

1.35 (6H, singlet);

1.43 (3H, singlet);

1.7-2.3 (2H, nd);

1.79 (2H, singlet);

2.27 (3H, singlet);

2.70 (2H, broad triplet, J = 6Hz);

3.07 (1H, doublet of doublets, J = 7.5 & 15Hz);

3.32 (1H, doublet of doublets, J = 7.5 & 15Hz);

3.91 (2H, AB type, J = 9Hz);

4.18 (2H, quartet, J = 7Hz);

4.37 (1H, triplet, J = 7Hz);

6.72 (1H, singlet);

6.85 (1H, singlet);

6.86 (2H, doublet, J = 9Hz);

7.16 (2H, doublet, J = 9Hz).

PREPARATION 24

6-Acetoxy-2-(4-aminophenoxymethyl)-2-methyl-4-oxo-7-(1,1,3,3-tetramethylbutyl)chroman (Step D2)

12.3 g of 6-acetoxy-2-methyl-2-(4-nitrophenoxymethyl)-7-(1,1,3,3-tetramethylbutyl)chroman-4-one (prepared as described in Preparation 19) were dissolved in a mixture of 200 ml of methanol and 20 ml of benzene, and then catalytically reduced for 6 hours at room temperature, in the presence of 2.4 g of 10% w/w palladium-on-carbon, under 1 atmosphere (about 1 bar) pressure of hydrogen. The catalyst was filtered off, and the filtrate was condensed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography, eluted with a 4:1 by volume mixture of benzene and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.29 (developing solvent, benzene:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.78 (9H, singlet);

1.37 (6H, singlet);

1.52 (3H, singlet);

1.83 (2H, singlet);

2.30 (3H, singlet);

2.66 (1H, doublet, J = 17Hz);

3.10 (1H, doublet, J = 17Hz);

3.4 (2H, broad singlet, disappeared on adding heavy water);

3.92 & 4.06 (2H, AB type, J = 9Hz);

6.58 (2H, doublet, J = 9Hz);

6.76 (2H, doublet, J = 9Hz);

7.00 (1H, singlet);

7.50 (1H, singlet).

PREPARATION 25

Ethyl 3-{4-[6-acetoxy-2-methyl-4-oxo-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]phenyl}-2-chloropropionate (Step D3)

Following the same procedure as described in Preparation 18, 9 g of 6-acetoxy-2-(4-aminophenoxymethyl)-2-methyl-7-(1,1,3,3-tetramethylbutyl)-chroman-4-one (prepared as described in Preparation 24), 1.8 g of sodium nitrite, 10 ml of concentrated hydrochloric acid, 20 g of ethyl acrylate, 0.3 g of cuprous oxide, 100 ml of acetone and about 8 ml of water were reacted, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.32 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.78 (9H, singlet);

1.23 (3H, triplet, J = 7 Hz);

1.38 (6H, singlet);

1.53 (3H, singlet);

1.85 (2H, singlet);

2.30 (3H, singlet);

2.69 (1H, doublet, J = 17Hz);

3.08 (1H, doublet of doublets, J = 7.5 & 15Hz);

3.10 (1H, doublet, J = 17Hz);

3.32 (1H, doublet of doublets, J = 7.5 & 15Hz);

3.99 & 4.12 (2H, AB type, J = 10.5Hz);

4.18 (2H, quartet, J = 7Hz);

4.36 (1H, triplet, J = 7Hz);

6.82 (2H, doublet, J = 9Hz);

7.01 (1H, singlet);

7.16 (2H, doublet, J = 9Hz);

7.52 (1H, singlet).

PREPARATION 26

5-{4-[6-Acetoxy-2-methyl-4-oxo-7-(1,1,3,3-tetramethylbutyl)chroman-2-ylmethoxy]benzyl}-2-iminothiazolidin-4-one

After completing the silica gel column chromatography described in Example 6, the column was further eluted with a 4:1 by volume mixture of benzene and tetrahydrofuran, to give the title compound melting at 125-130°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

0.77 (9H, singlet);

1.39 (6H, singlet);

1.53 (3H, singlet);

1.89 (2H, singlet);

2.34 (3H, singlet);

2.6-3.0 (1H, nd);

2.75 (1H, doublet, J = 16Hz);

3.13 (1H, doublet, J = 16Hz);

3.40 (1H, doublet of doublets, J = 4 & 14Hz);

4.17 (2H, singlet);

4.48 (1H, doublet of doublets, J = 4 & 10Hz);

6.87 (2H, doublet, J = 9Hz);

7.01 (1H, singlet);

7.20 (2H, doublet, J = 9Hz);

7.46 (1H, singlet);

7.8-8.7 (2H, broad, disappeared on adding heavy water).

PREPARATION 27

Ethyl 2-(3,7-dimethyloctyl)-6-methoxymethoxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane)-2-carboxylate (Step E4)

17.7 ml of a hexane solution containing 1.62 mmole/ml of butyllithium were added dropwise under a nitrogen stream at a temperature between -60°C and -50°C to a solution of 2.9 g of diisopropylamine in 30 ml of tetrahydrofuran, and the mixture was allowed to stand for 10 minutes at room temperature. 10 ml of tetrahydrofuran containing 6 g of ethyl 6-methoxymethoxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane)-2-carboxylate (prepared as described in Preparation 3) were added dropwise to the reaction mixture at -60°C. The reaction mixture was stirred for 1 hour, and then 5 ml of tetrahydrofuran containing 6.4 g of 3,7-dimethyloctyl bromide were added dropwise, and the mixture was stirred for a further 1 hour at the same temperature. After the mixture had been stirred for a further 1 hour at room temperature and then stirred for 1.5 hours at 45-50°C, the resulting mixture was allowed to stand overnight at room temperature. The reaction mixture was then poured into ice-water and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography, eluted with a 10:1 by volume mixture of hexane and ethyl acetate, to give the title compound as a pale yellow oily substance.

Rf value on silica gel thin layer chromatography = 0.57 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.87 (9H, doublet, J = 7Hz);

1.0-2.3 (14H, multiplet);

1.17 (3H, triplet, J = 7Hz);

2.17 (3H, singlet);

2.21 (3H, singlet);

2.3-2.9 (2H, nd);

2.62 (1H, doublet, J = 14Hz);

2.83 (3H, singlet);

2.97-3.5 (2H, multiplet);

3.59 (3H, singlet);

3.73 (1H, doublet, J = 14Hz);

4.03 (1H, quartet, J = 7Hz);

4.07 (1H, quartet, J = 7Hz);

4.88 (2H, singlet).

PREPARATION 28

2-(3,7-Dimethyloctyl)-2-hydroxymethyl-6-methoxymethoxy-5,7,8-trimethylchromanspiro-4, 2'-(1',3'-dithiane) (Step E5)

20 ml of tetrahydrofuran containing 4 g of ethyl 2-(3,7-dimethyloctyl)-6-methoxymethoxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane)-2-carboxylate (prepared as described in Preparation 27) were added dropwise under a nitrogen stream and whilst ice-cooling to a mixture of 0.41 g of lithium aluminium hydride and 30 ml Of tetrahydrofuran, and the mixture was then stirred for 3 hours at room temperature. About 10 ml of ethyl acetate and about 30 ml of 5% w/v aqueous hydrochloric acid were then added, and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate. The organic layer and the ethyl acetate extract were combined and washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure to giv the title compound as a pale yellow oil.

Rf value on silica gel thin layer chromatography = 0.36 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.87 (9H, doublet, J = 7Hz);

1.0-2.0 (12H, multiplet);

2.0-2.5 (2H, nd);

2.08 (3H, singlet);

2.20 (3H, singlet);

2.34 (1H, broad singlet, disappeared on adding heavy water);

2.5-3.0 (3H, multiplet);

2.92 (3H, singlet);

3.0-3.6 (4H, multiplet);

3.61 (3H, singlet);

3.76 (1H, doublet of doublets, J = 6 & 12Hz);

4.89 (2H, singlet).

PREPARATION 29

2-(3,7-Dimethyloctyl)-6-methoxymethoxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chromanspiro-4,2'-(1',3'-dithiane) (Step E6)

0.48 g of a 55% w/w suspension of sodium hydride in mineral oil were added to a mixture of 3.6 g of 2-(3,7-dimethyloctyl)-2-hydroxymethyl-6-methoxymethoxy-5,7,8-trimethylchromanspiro-4,2'-(1',3'-dithiane) (prepared as described in Prepartion 28) and 30 ml of dimethylformamide under a nitrogen stream at room temperature, and the resulting mixture was heated at 50°C for 2 hours. A mixture of 1.66 g of p-chloronitrobenzene and 3 ml of benzene was added dropwise, and then the mixture was heated at 50°C for 2 hours. The reaction mixture was then poured into water and extracted with benzene. The extract was washed with water and dried ov r anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography, eluted with a 50:1 by volume mix-

ture of benzene and ethyl acetate, to give the tital compound.

Rf value on silica gel thin layer chromatography = 0.55 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.87 (9H, doublet, J = 7Hz);

1.0-2.3 (14H, multiplet);

2.08 (3H, singlet);

2.21 (3H, singlet);

2.3-3.0 (3H, multiplet);

2.89 (3H, singlet);

3.0-3.6 (3H, multiplet);

3.61 (3H, singlet);

3.99 (1H, doublet, J = 9Hz);

4.45 (1H, doublet, J = 9Hz);

4.89 (2H, singlet);

6.92 (2H, doublet, J = 9Hz);

8.17 (2H, doublet, J = 9Hz).

PREPARATION 30

2-(3,7-Dimethyloctyl)-6-hydroxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one (Steps E7 and A3, Deprotection)

A mixture of 3.4 g of 2-(3,7-dimethyloctyl)-6-methoxymethoxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chromanspiro-4,2'-(1',3'-dithiane) (prepared as described in Preparation 29), 2.2 g of mercuric chloride, 1.7 g of mercuric oxide, 10 ml of tetrahydrofuran, 27 ml of methanol and 3 ml of water was heated under reflux for 2 hours. Benzene was then added to the reaction mixture, and the insoluble residue was filtered off. The filtrate was washed with an aqueous ammonium sulphate solution, and then with water, and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. 30 ml of benzene, 10 ml of acetic acid and 0.5 ml of 10% w/v aqueous sulphuric acid were added to the residue, and the mixture was heated under reflux for 30 minutes. The reaction mixture was then poured into water and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography, eluted with a 100:3 by volume mixture of benzene and ethyl acetate, and the resulting crystals were recrystallized from a mixture of benzene and hexane to give the title compound, melting at 121-123°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.85 (9H, doublet, J = 7Hz);

1.0-1.7 (10H, multiplet);

1.7-2.1 (2H, multiplet);

2.11 (3H, singlet);

2.21 (3H, singlet);

2.55 (3H, singlet);

2.78 & 2.98 (2H, AB type, J = 16Hz);

4.16 (2H, singlet);

4.57 (1H, singlet, disappeared on adding heavy water);

7.96 (2H, doublet, J = 9Hz);

8.20 (2H, doublet, J = 9Hz).

PREPARATION 31

6 Acetoxy -2-(3,7-dimethyloctyl)-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one (Step A3, Acylation)

Following the same procedure as described in Preparation 16, 1.8 g of 2-(3,7-dimethyloctyl)-6-hydroxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)-chroman-4-one (prepared as described in Preparation 30), 0.5 g of acetic anhydride, 5 ml of pyridine and 10 ml of benzene were reacted, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.41 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.85 (9H, doublet, J = 7Hz);

1.0-2.0 (12H, multiplet);

2.08 (3H, singlet);

2.11 (3H, singlet);

2.33 (3H, singlet);

2.41 (3H, singlet);

2.80 & 3.00 (2H, AB type, J = 16Hz);

4.17 (2H, singlet);

6.95 (2H, doublet, J = 9Hz);

8.20 (2H, doublet, J = 9Hz).

PREPARATION 32

6-Acetoxy-2-(4-aminophenoxymethyl)-2-(3,7-dimethyloctyl-5,7,8-trimethylchroman-4-one (Step D2)

Following the same procedure as described in Preparation 24, 1.95 g of 6-acetoxy-2-(3,7-dimethyloctyl)-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 31) was treated with 0.4 g of 10% w/w palladium-on-carbon, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.31 (developing solvent, benzene:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.85 (9H, doublet, J = 7Hz);

1.0-2.0 (12H, multiplet);

2.09 (3H, singlet);

2.13 (3H, singlet);

2.32 (3H, singlet);

2.41 (3H, singlet);

2.77 & 3.00 (2H, AB type, J = 16Hz);

3.4 (2H, broad singlet, disappeared on adding heavy water);

3.99 (2H, singlet);

6.60 (2H, doublet, J = 9Hz);

6.70 (2H, doublet, J = 9Hz).

PREPARATION 33

Ethyl 3-{4-[6-acetoxy-2-(3,7-dimethyloctyl)-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy]phenyl}-2-chloropropionate (Step D3)

Following the same procedure as described in Preparation 18, 1.6 g of 6-acetoxy-2-(4-aminophenoxymethyl)-2-(3,7-dimethyloctyl)-5,7,8-trimethylchroman-4-one (prepared as described in Preparation 32), 0.28 g of sodium nitrite, 1.7 ml of concentrated hydrochloric acid, 3.3 ml of ethyl acrylate and 0.1 g of cuprous oxide were reacted, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.45 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.86 (9H, doublet, J = 7Hz);

1.0-2.0 (12H, multiplet);

1.24 (3H, triplet, J = 7Hz);

2.09 (3H, singlet);

2.13 (3H, singlet);

2.33 (3H, singlet);

2.42 (3H, singlet);

2.80 & 2.98 (2H, AB type, J = 16Hz);

3.07 (1H, doublet of doublets, J = 7 & 14Hz);

3.31 (1H, doublet of doublets, J = 7 & 14Hz);

4.06 (2H, singlet);

4.18 (2H, quartet, J = 7Hz);

4.37 (1H, triplet, J = 7Hz);

6.83 (2H, doublet, J = 9Hz);

7.15 (2H, doublet, J = 9Hz).

PREPARATION 34

6-Methoxymethoxy-2,5,7,8-tetramethyl-2-(5-nitropyridin-2-yloxymethyl)chroman (Step A2, Introduction of Aromatic group)

0.96 g of a 55% w/w suspension of sodium hydride in mineral oil was washed 4 times with cyclohexane and then slowly added to a mixture of 5.0 g of 2-hydroxymethyl-6-methoxymethoxy-2,5,7,8-tetramethylchroman (prepared as described in Preparation 1 of copending EP-A 0139421) and 20 ml of dimethylformamide, under a nitrogen stream at room temperature. The reaction mixture was heated at 50°C for 10 minutes and then cooled to 10°C. 4.2 g of 2-chloro-5-nitropyridine were then added in limited amounts. The reaction mixture was allowed to stand overnight at room temperature and poured into water. The resulting mixture was extracted with benzene. The extract was washed with water and dried over sodium sulphate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography, elute with a 25:1 by volume mixture of benzene and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.56 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.40 (3H, singlet);

1.7-2.3 (2H, multiplet);

2.02 (3H, singlet);

2.17 (6H, singlet);

2.65 (2H, broad triplet, J = 6Hz);

3.61 (3H, singlet);

4.51 (2H, singlet);

4.88 (2H, singlet);

6.87 (1H, doublet, J = 9Hz);

8.37 (1H, doublet of doublets, J = 9 & 3Hz);

9.06 (1H, doublet, J = 3Hz).

PREPARATION 35

6-Hydroxy-2,5,7,8-tetramethyl-2-(5-nitropyridin-2-yloxymethyl)chroman (Step A3, Deprotection)

1 g of 10% w/v aqueous sulphuric acid was added to 45 ml of acetic acid containing 5.2 g of 6-methoxymethoxy-2,5,7,8-tetramethyl-2-(5-nitropyridin-2-yloxymethyl)chroman (prepared as described in Prepation 34), and the resulting mixture was heated at 55-58°C for 15 minutes. The reaction mixture was cooled, poured into a mixture of 75 g of sodium bicarbonate and 75 g of ice, and then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The residue gave the title compound as a light-brown oil.

Rf value on silica gel thin layer chromatography = 0.46 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.39 (3H, singlet);

1.7-2.3 (2H, multiplet);

2.05 (3H, singlet);

2.11 (3H, singlet);

2.15 (3H, singlet);

2.67 (2H, broad triplet, J = 6Hz);

4.19 (1H, singlet, disappeared on adding heavy water);

4.50 (2H, singlet),

6.85 (1H, doublet, J = 9Hz);

8.36 (1H, doublet of doublets, J = 9 & 3Hz);

9.06 (1H, doublet, J = 3Hz).

PREPARATION 36

6-Acetoxy-2,5,7,8-tetramethyl-2-(5-nitropyridin-2-yloxymethyl)chroman (Step A3, Acylation)

Following the same procedure as described in Preparation 16, 5.2 g of 6-hydroxy-2,5,7,8-tetramethyl-2-(5-nitropyridin-2-yloxymethyl)-chroman (prepared as described in Preparation 35), 3 ml of acetic anhydride, 3 ml of pyridine and about 20 ml of benzene were reacted to give the title compound.

Rf value on silica gel thin layer chromatography = 0.52 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.40 (3H, singlet);

1.7-2.3 (2H, multiplet);

2.02 (9H, singlet);

2.32 (3H, singlet);

2.69 (2H, broad triplet, J=6Hz);

4.52 (2H, AB type, J=12Hz);

6.86 (1H, doublet, J=9Hz);

8.36 (1H, double of doublets, J=9 & 3Hz);

9.07 (1H, doublet, J=3Hz).

PREPARATION 37

6-Acetoxy-2-(5-aminopyridin-2-yloxymethyl)-2,5,7,8-tetramethylchroman (Step A3, Hydrogenation)

6 g of 6 acetoxy-2,5,7,8-tetramethyl-2-(5-nitropyridin-2-yloxymethyl)chroman (prepared as described in Preparation 36) were dissolved in a mixture of 80 ml of methanol and 15 ml of benzene, and, in the presence of 1.5 g of 10% w/w palladium-on-carbon, were catalytically reduced at room temperature for about 20 hours under about 1 atmosphere (about 1 bar) pressure of hydrogen. The catalyst was filtered off, and the filtrate was condensed by evaporation under reduced pressure, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.04 (dev loping solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.39 (3H, singlet);

1.6-2.4 (2H, multiplet);

1.97 (3H, singlet);

2.01 (3H, singlet);

2.07 (3H, singlet);

2.30 (3H, singlet);

2.64 (2H, broad triplet, J=6Hz);

3.9 (2H, broad singlet, disappeared on adding heavy water);

4.25 (2H, AB type, J=12Hz);

6.61 (1H, doublet, J=9Hz);

7.02 (1H, doublet of doublets, J=9 & 3Hz);

7.64 (1H, doublet, J=3Hz).

PREPARATION 38

Ethyl 3-[2-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)pyridin-5-yl]-2-chloropropionate (Step A4)

Following the same procedure as described in Preparation 18, 4.5 g of 6-acetoxy-2-(5-aminopyridin-2-yloxymethyl)-2,5,7,8-tetramethylchroman (prepared as described in Preparation 37), 1.1 g of sodium nitrite, 5 ml of concentrate hydrochloric acid, 10 g of ethyl acrylate, 175 mg of cuprous oxide, 40 ml of acetone and about 2.5 g of water were reacted, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.45 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.26 (3H, triplet, J=7.5Hz);

1.40 (3H, singlet);

1.7-2.3 (2H, multiplet);

1.99 (3H, singlet);

2.02 (3H, singlet);

2.07 (3H, singlet);

2.31 (3H, singlet);

2.65 (2H, broad triplet, J = 6Hz);

3.07 (1H, doublet of doublets, J = 13.5 & 7.5Hz);

3.30 (1H, doublet of doublets, J = 13.5 & 7.5Hz);

4.0-4.5 (5H, multiplet);

6.72 (1H, doublet, J = 9Hz);

7.48 (1H, doublet of doublets, J = 9 & 3Hz);

8.02 (1H, doublet, J = 3Hz).

PREPARATION 39

5-Acetoxy-4-t-butyl-2-hydroxyacetophenone

A mixture of 100 g of t-butylhydroquinone, 130 ml of acetic anhydride and 1 kg of a boron trifluoride-acetic acid complex salt (boron trifluoride content 40%) was heated for 2 hours at 60°C, whilst stirring, and was then heated for a further 2 hours at 90°C. The reaction mixture was cooled, and then it was poured into 3 litres of ice-water and extracted with benzene. The benzene extract was washed with a saturated aqueous solution of sodium bicarbonate and then with water and dried over anhydrous sodium sulphate. The solvent was distilled off and the resulting oily residue was purified by silica gel column chromatography eluted with benzene, to give the title compound, melting at 86.5-87.5°C.

PREPARATION 40

6-Acetoxy-7-t-butyl-2-methyl-2-(2-methyl-5-nitrophenoxymethyl)chroman-4-one (Step D1)

Following the same procedure as described in Preparation 19, 4.78 g of 5-acetoxy-4-t-butyl-2-hydroxyacetophenone (prepared as described in Preparation 39), 4.0 g of 1-(2-methyl-5-nitrophenoxy)propan-2-one, 2.0 g of pyrrolidine, 50 ml of benzene, 4 ml of acetic anhydride and 50 ml of pyridine were reacted, to give the title compound, as a slightly red, foamy substance.

Rf value on silica gel thin layer chromatography = 0.24 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum [$(CH_3)_2CO$] δ ppm:

1.32 (9H, singlet);

1.63 (3H, singlet);

2.17 (3H, singlet);

2.32 (3H, singlet);

2.90 (1H, doublet, J = 16.5Hz);

3.15 (1H, doublet, J = 16.5Hz);

4.43 (2H, AB type, J = 12Hz);

6.97 (1H, singlet);

7.38 (1H, doublet, J = 8Hz);

7.45 (1H, singlet);

7.70-7.90 (2H, multiplet).

PREPARATION 41

6-Acetoxy-2-(5-amino-2-methylphenoxymethyl)-7-t-butyl-2-methylchroman-4-one (Step D2)

Following the same procedure as described in Preparation 24, hydrogenation of 7.3 g of 6-acetoxy-7-t-butyl-2-methyl-2-(2-methyl-5-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 40) in the presence of 1 g of 10% w/w palladium-on-carbon and 100 ml of ethanol gave the title compound as a slightly red, foamy substance.

Rf value on silica gel thin layer chromatography = 0.13 (developing solvent, benzene:ethyl acetate = 5:1 by volume).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.33 (9H, singlet);

1.58 (3H, singlet);

1.95 (3H, singlet);

2.31 (3H, singlet);

2.80 (1H, doublet, J = 16.5Hz);

3.10 (1H, doublet, J = 16.5Hz);

4.06 (2H, singlet);

3.90-4.70 (2H, broad, disappeared on adding heavy water);

6.18 (1H, doublet of doublets, J = 8 & 1.5Hz);

6.28 (1H, doublet, J = 1.5Hz);

6.78 (1H, doublet, J = 8Hz);

7.00 (1H, singlet);

7.47 (1H, singlet).

PREPARATION 42

Ethyl 3-[3-(6-acetoxy-7-t-butyl-2-methyl-4-oxochroman-2-ylmethoxy)-4-methylphenyl]-2-chloropropionate (Step D3)

Following the same procedure as described in Preparation 25, 5.53 g of 6-acetoxy-2-(5-amino-2-methylphenoxymethyl)-7-t-butyl-2-methylchroman-4-one (prepared as described in Preparation 41), 1.2 g of sodium nitrite, 2.4 ml of concentrated hydrochloric acid, 14 ml of ethyl acrylate, 190 ml of cuprous oxide and 50 ml of acetone were reacted, to give the title compound as a pale yellow oil.

Rf value on silica gel thin layer chromatography = 0.41 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.22 (3H, triplet, J = 7.5Hz);

1.32 (9H, singlet);

1.57 (3H, singlet);

2.10 (3H, singlet);

2.30 (3H, singlet);

2.74 (1H, doublet, J = 17Hz);

2.94-3.25 (1H, nd);

3.08 (1H, doublet, J = 17Hz);

3.33 (1H, doublet of doublets, J = 7 & 14Hz);

3.99 & 4.11 (2H, AB type, J = 10Hz);

4.18 (2H, quartet, J = 7.5Hz);

4.40 (1H, triplet, J = 7Hz);

6.65-6.85 (2H, nd);

6.99 (1H, singlet);

7.07 (1H, doublet, J = 7.5Hz);

7.50 (1H, singlet).

PREPARATION 43

6-Acetoxy-2-hydroxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one (Step H1)

A solution of 3 g of potassium t-butoxide in 100 ml of tetrahydrofuran was added dropwise to a solution of 15 g of 3-acetoxy-2,4,5-trimethyl-6-(4-nitrophenoxyacetoxy)acetophenone in 1 litre of tetrahydrofuran, whilst ice-cooling, and the resulting mixture was stirred at the same temperature for 2.5 hours. The reaction mixture was then poured into a mixture of ethyl acetate and an aqueous solution of sodium chloride, and the organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off. The residue was purified by silica gel column chromatography, eluted with a 1:1 by volume mixture of hexane and ethyl acetate, to give the title compound, melting at 204-207°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:

2.05 (3H, singlet);

2.11 (3H, singlet);

2.34 (6H, singlet);

2.76 (1H, doublet, J = 17Hz);

3.24 (1H, doublet, J = 17Hz);

4.28 & 4.50 (2H, AB type, J = 10Hz);

7.24 (2H, doublet, J = 9Hz);

7.30 (1H, singlet, disappeared on adding heavy water);

8.24 (2H, J = 9Hz).

PREPARATION 44

6-Acetoxy-2-(4-aminophenoxymethyl)-2-hydroxy-5,7,8-trimethylchroman-4-one (Step H2)

Following the same procedure as described in Preparation 24, 7 g of 6-acetoxy-2-hydroxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 43) were treated with 5 g of 10% w/w palladium-on-carbon, 100 ml of tetrahydrofuran and 100 ml of ethanol, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.48 (developing solvent, ethyl acetate).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

2.08 (3H, singlet);

2.10 (3H, singlet);

2.32 (3H, singlet);

2.41 (3H, singlet);

2.78 & 3.03 (2H, AB type, J = 16Hz);

3.4-4.3 (3H, broad singlet, disappeared on adding heavy water);

3.98 & 4.12 (2H, AB type, J = 10Hz);

6.62 (2H, doublet, J = 9Hz);

6.80 (2H, doublet, J = 9Hz).

PREPARATION 45

Ethyl 3-[4-(6-acetoxy-2-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate (Step H3)

Following the same procedure as described in Preparation 18, 3.4 g of 6-acetoxy-2-(4-aminophenoxymethyl)-2-hydroxy-5,7,8-trimethylchroman-4-one (prepared as described in Preparation 44), 40 ml of acetone, 5ml of 35% w/v aqueous hydrochloric acid, 1.2 g of sodium nitrite, 1.6 ml of water, 13 g of ethyl acrylate and 0.32 g of cuprous oxide were reacted, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.20 (developing solvent, hexane:ethyl acetate = 2:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.24 (3H, triplet, J = 7Hz);

2.09 (6H, singlet);

2.33 (3H, singlet);

2.42 (3H, singlet);

2.5-3.6 (4H, nd);

3.9-4.6 (5H, nd);

6.93 (2H, doublet, J = 9Hz);

7.20 (2H, doublet, J = 9Hz).

PREPARATION 46

Ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloro-2-methylpropionate (Step A4)

Following the same procedure as described in Preparation 18, 2 g of 6-acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman (prepared as described in Preparation 50), 25 ml of acetone, 3 ml of 35% w/v aqueous hydrochloric acid, 0.7 g of sodium nitrite, 1 ml of water, 8 g of ethyl methacrylate and 0.2 g of cuprous oxide were reacted, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.54 (developing solvent, hexane:ethyl acetate = 2:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.29 (3H, triplet, J = 7Hz);

1.43 (3H, singlet);

1.68 (3H, singlet);

1.98 (3H, singlet);

2.03 (3H, singlet);

2.09 (3H, singlet);

2.32 (3H, singlet);

1.5-2.5 (2H, nd);

2.62 (2H, broad triplet, J = 7Hz);

3.18 & 3.36 (2H, AB type, J = 17Hz);

3.84 & 3.98 (2H, AB type, J = 9Hz);

4.21 (2H, quartet, J = 7Hz);

6.84 (2H, doublet, J = 9Hz);

7.14 (2H, doublet, J = 9Hz).

PREPARATION 47

6-Acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one (Step D1)

(a) A mixture of 17.7 g of 5-acetoxy-2-hydroxy-3,4,6,-trimethylacetophenone, 14.6 g of 4-nitrophenoxyacetone, 7.5 g of pyrrolidine and 60 ml of benzene was allowed to stand for 1 day at room temperature, and then heated under reflux for 7 hours using a water separator. Water and ethyl acetate were added to the reaction mixture. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was distilled off and the resulting residue was purified by silica gel column chromatography using a 2:1 by volume mixture of hexane and ethyl acetate as eluent, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.17 (developing solvent, hexane:ethyl acetate = 3:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.56 (3H, singlet);

2.10 (6H, singlet);

2.36 (3H, singlet);

2.43 (3H, singlet);

2.70 (1H, doublet, J = 15Hz);

3.06 (1H, doublet, J = 15Hz);

4.11 (1H, doublet, J = 10Hz);

4.24 (1H, doublet, J = 10Hz);

6.98 (2H, doublet, J = 9Hz);

8.20 (2H, doublet, J = 9Hz).

(b) A mixtur of the sam components as mentioned in (a), but containing piperidine instead of pyrrolidine, was heated under reflux for 3 hours using a water separator. 5% w/v aqueous hydrochloric acid was added, and the reaction mixture was extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off to give the title compound. The Rf value and nuclear magnetic resonance spectrum of this compound accorded with those of the compound obtained in - (a).

(c) In a similar manner to (b), the use of morpholine instead of piperidine afforded the title compound. The Rf value and nuclear magnetic resonance spectrum of this compound accorded with those of the compound obtained in (a).

(d) A mixture of the same components as mentioned in (a), but containing morpholine instead of pyrrolidine, and toluene instead of benzene, was heated under reflux for 1 hour. Then, in a similar manner to (b), the title compound was obtained. The Rf value and nuclear magnetic resonance spectrum of this compound accorded with those of the compound obtained in (a).

PREPARATION 48

6-Acetoxy-4-hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman (Step F1)

160 mg of sodium borohydride were added to a mixture of 1.8 g of 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 47), 15 ml of methanol and 1 ml of benzene in an ice bath, and the mixture was stirred for 30 minutes. The reaction mixture was then poured into ice-water, neutralized with 10% w/v aqueous hydrochloric acid and extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography eluted with a 9:1 by volume mixture of benzene and ethyl acetate, to give crystals. These crystals were recrystallized from a mixture of benzene and hexane to give the title compound, melting at 139-141°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.56 (3H, singlet);

2.05 (6H, singlet);

2.0-2.4 (2H, nd);

2.19 (3H, singlet);

2.33 (3H, singlet);

4.10 (2H, AB type, J = 9Hz);

5.0 (1H, doublet of doublets, J = 3 & 9Hz);

7.03 (2H, doublet, J = 9Hz);

8.23 (2H, doublet, J = 9Hz).

PREPARATION 49

6-Acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)-2H-chromene (Step F3)

Following the procedure described in Preparation 57, 160 mg of 6-acetoxy-4-hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman (prepared as described in Preparation 48), 10 mg of p-toluenesulphonic acid and 2 ml of benzene gave the title compound.

Rf value on silica gel thin layer chromatography = 0.49 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.59 (3H, singlet);

2.03 (3H, singlet);

2.05 (3H, singlet);

2.09 (3H, singlet);

2.33 (3H, singlet);

4.10 (2H, AB type, J = 9Hz);

5.73 (1H, doublet, J = 10Hz);

6.73 (1H, doublet, J = 10Hz);

6.96 (2H, doublet, J = 9Hz);

8.22 (2H, doublet, J = 9Hz).

PREPARATION 50

6-Acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman (Step F5)

Following the procedure described in Preparation 58, 100 mg of 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)-2H-chromene (prepared as described in Preparation 49) were dissolved in 2 ml of methanol and, in the presence of 20 mg of 10% w/w palladium-on-carbon, the compound was reduced under 1 atmosphere (about 1 bar) pressure of hydrogen, to give the title compound melting at 138-140°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.42 (3H, singlet);

2.00 (3H, singlet);

about 2 (2H, multiplet);

2.04 (3H, singlet);

2.10 (3H, singlet);

2.31 (3H, singlet);

2.6 (2H, broad triplet, J = 6Hz);

3.37 (2H, broad, disappeared on adding heavy water);

3.80 & 3.95 (2H, AB type, J = 9Hz);

6.62 (2H, doublet, J = 7.5Hz);

6.78 (2H, doublet, J = 7.5Hz).

PREPARATION 51

Ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate (Step A4)

17.5 g of 6-acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman (prepared as described in Preparation 50) were dissolved in a mixture of 130 ml of acetone and 30 ml of water. 13 ml of concentrated hydrochloric acid, and then 8.5 ml of water containing 4.3 g of sodium nitrite, were added dropwise to this solution in an ice bath. A further 37.3 ml of ethyl acrylate were then added dropwise, and then the reaction mixture was heated to 40-43°C; at this temperature, 680 mg of cuprous oxide were added slowly. After about 30 minutes, nitrogen generation finished. The reaction mixture, which had separated into two layers, was mixed

with benzene to extract the organic layer. The benzene extract was washed with a saturated aqueous solution of sodium chloride and the dried over anhydrous sodium sulphate. The solvent was distilled off and the resulting dark brown oil was subjected to silica gel column chromatograph. After the first elution with a 1:1 by volume mixture of benzene and cyclohexane, the title compound was obtained from the next elution with a 2:1 by volume mixture of benzene and cyclohexane and from the subsequent elution with benzene alone.

Rf value on silica gel thin layer chromatography = 0.39 (developing solvent, benzene:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.23 (3H, triplet, J=7.5Hz);

1.42 (3H, singlet);

about 2 (2H, multiplet);

1.98 (3H, singlet);

2.04 (3H, singlet);

2.09 (3H, singlet);

2.31 (3H, singlet);

2.6 (2H, broad triplet, J=6Hz);

3.05 (1H, doublet of doublets, J=15 & 7.5Hz);

3.31 (1H, doublet of doublets, J=15 & 7.5Hz);

3.83 & 3.99 (2H, AB type, J=9Hz);

4.18 (2H, quartet, J=7.5Hz);

4.38 (1H, triplet, J=7.5Hz);

6.85 (2H, doublet, J=9Hz);

7.14 (2H, doublet, J=9Hz).

PREPARATION 52

6-Hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one (Step D1)

A mixture of 3.9 g of 2,5-dihydroxy-3,4,6-trimethylacetophenone, 3.9 g of 4-nitrophenoxyacetone, 2.0 g of pyrrolidine and 15 g of toluene was allowed to stand for 2 days at room temperature. Dilute hydrochloric acid was then added to th reaction mixture and the mixture was extracted with diethyl ether. The aqueous layer was further extracted with ethyl acetate. The ethyl acetate extract and the ethereal extract were combined and dried over anhydrous sodium sulphate. The solvent was distilled off and hexane was added to the resulting residue. The crystals which separated were collected by filtration and purified by silica gel column chromatography using a 5:1 by volume mixture of hexane and ethyl acetate as eluent. Recrystallization of the product from ethyl acetate gave the title compound, melting at 199-204°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:

1.43 (3H, singlet);

2.01 (3H, singlet);

2.14 (3H, singlet);

2.46 (3H, singlet);

2.67 (1H, doublet, J=16Hz);

3.03 (1H, doublet, J=16Hz);

4.31 (2H, singlet);

7.19 (2H, doublet, J=9Hz);

7.92 (1H, singlet);

8.21 (2H, doublet, J=9Hz).

PREPARATION 53

7-t-Butyl-6-hydroxy-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one (Step D1)

Following the procedure described in Preparation 52, the title compound was prepared from 2.0 g of 4-t-butyl-2,5-dihydroxyacetophenone, 1.9 g of 4-nitrophenoxyacetone, 1.0 g of pyrrolidine and 10 ml of benzene. The compound obtained melted at 205-209°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.39 (3H, singlet);

1.53 (9H, singlet);

2.70 (1H, doublet, J=16.5Hz);

3.05 (1H, doublet, J = 16.5Hz);

4.37 (2H, singlet);

6.80 (1H, singlet);

7.18 (2H, doublet, J = 10Hz);

7.22 (1H, singlet);

8.22 (2H, doublet, J = 10Hz);

8.31 (1H, singlet, disappeared on adding heavy water).

PREPARATION 54

6-Acetoxy-7-t-butyl-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one

A mixture of 1.7 g of 7-t-butyl-6-hydroxy-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 53), 1 ml of acetic anhydride and 10 ml of pyridine was allowed to stand for 1 day at room temperature. The reaction mixture was then poured into ice-water, stirred for 2 hours and extracted with benzene. The benzene extract was washed with 3N aqueous hydrochloric acid, water, a saturated aqueous solution of sodium bicarbonate and water in that order, and then dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure and the resulting residue was recrystallized from a mixture of benzene and ethyl acetate (about 10:1 by volume) to give the title compound, melting at 82-84°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.33 (9H, singlet);

1.57 (3H, singlet);

2.33 (3H, singlet);

2.82 (1H, doublet, J = 16.5Hz);

3.13 (1H, doublet, J = 16.5Hz);

4.42 (2H, singlet);

6.93 (1H, singlet);

7.25 (2H, doublet, J = 9Hz);

7.44 (1H, singlet);

8.22 (2H, doublet, J = 9Hz).

PREPARATION 55

7-t-Butyl-4,6-dihydroxy-2-methyl-2-(4-nitrophenoxymethyl)chroman (Step F1)

A solution of 3.0 g of 6-acetoxy-7-t-butyl-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 54) in 20 ml of tetrahydrofuran was dropped into a suspension containing 0.3 g of sodium borohydride in 10 ml of methanol whilst stirring over an ice bath. After the whole of the solution had been added, the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was then ice-cooled again, acidified weakly with 10% w/v aqueous hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed by evaporation under reduced pressure to give crystals. Recrystallization of these crystals from a mixture of benzene and petroleum ether gave the title compound, melting at 194-201°C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.34 (9H, singlet);

1.50 (3H, singlet);

1.88 (1H, doublet of doublets, J = 13.5 & 9Hz);

2.45 (1H, doublet of doublets, J = 13.5 & 6Hz);

2.78 (1H, singlet, disappeared on adding heavy water);

4.15 (2H, singlet);

4.75 (1H, multiplet);

6.62 (1H, singlet);

6.91 (1H, singlet);

7.15 (2H, doublet, J = 9Hz;

8.20 (2H, doublet, J = 9Hz).

PREPARATION 56

4,6-Diacetoxy-7-t-butyl-2-methyl-2-(4-nitrophenoxymethyl)chroman (Step F2)

3 ml of acetic anhydride were added to a mixture of 2.0 g of 7-t-butyl-4,6-dihydroxy-2-methyl-2-(4-nitrophenoxymethyl)chroman (prepared as described in Preparation 55) and 20 ml of pyridine, and the mixture was heated for 3 hours at 50°C. The reaction mixture was then dissolved in benzene and washed with 3N aqueous hydrochloric acid, water, a saturated aqueous solution of sodium bicarbonate and water in that order, and then dried over anhydrous sodium sulphate. The solvent was distilled off to give the title compound as a slightly yellow oil.

Rf value on silica gel thin layer chromatography = 0.62 (developing solvent, benzene:ethyl acetate = 5:1 by volume).

Nuclear Magnetic Resonance Spectrum $[CD_3)_2CO]$ δ ppm:

1.31 (9H, singlet);

1.55 (3H, singlet);

1.77 (3H, singlet);

2.0-2.3 (1H, nd);

2.27 (3H, singlet);

2.45-2.7 (1H, nd);

4.20 & 4.38 (2H, AB type, J=10Hz);

5.85-6.10 (1H, multiplet);

6.87 (1H, singlet);

6.98 (1H, singlet);

7.20 (2H, doublet, J=9Hz);

8.30 (2H, doublet, J=9Hz).

PREPARATION 57

6-Acetoxy-7-t-butyl-2-m thyl-2-(4-nitrophenoxymethyl)-2H-chromene (Step F4)

A mixture of 2.4 g of 4,6-diacetoxy-7-t-butyl-2-methyl-2-(4-nitrophenoxymethyl)chroman (pr pared as described in Preparation 56), 0.1 g of p-toluenesulphonic acid monohydrate and 50 ml of benzene was heated under reflux for 1 hour. The reaction solution was cooled, washed with a saturated aqueous solution of sodium bicarbonate, and then with water, and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure, to give the title compound as a yellow oil.

Rf value on silica gel thin layer chromatography = 0.58 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum $[(CD_3)_2CO]$ δ ppm:

1.27 (9H, singlet);

1.54 (3H, singlet);

2.27 (3H, singlet);

4.28 (2H, singlet);

5.79 (1H, doublet, J=10Hz);

6.52 (1H, doublet, J=10Hz);

6.67 (1H, singlet);

6.76 (1H, singlet);

7.13 (2H, doublet, J=9Hz);

8.20 (2H, doublet, J=9Hz).

PREPARATION 58

6-Acetoxy-2-(4-aminophenoxymethyl)-7-t-butyl-2-methylchroman (Step F5)

2.1 g of 6-acetoxy-7-t-butyl-2-methyl-2-(4-nitrophenoxymethyl-2H-chromene (prepared as described in Preparation 57) were dissolved in a mixture of 20 ml of benzene and 2 ml of acetic acid, and the compound was reduced for 10 hours at room temperature, in the presence of 0.1 g of 10% w/w palladium-on-carbon, and under about 1 atmosphere (about 1 bar) pressure of hydrogen. The catalyst was filtered off, and the reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate and then with water, after

which it was dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure, and the resulting residue was purified by silica gel column chromatography, eluted with benzene, to give the title compound as a slightly brown oil.

Rf value on silica gel thin layer chromatography = 0.13 (developing solvent, benzene:ethyl acetate = 10:1 by volume).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2CO$] δ ppm:

1.30 (9H, singlet);

1.40 (3H, singlet);

1.7-2.2 (2H, nd);

2.27 (3H, singlet);

2.73 (2H, broad triplet, J = 7Hz);

3.89 (2H, singlet);

3.7-4.5 (2H, broad, disappeared on adding heavy water);

6.50-7.05 (6H, multiplet).

PREPARATION 59

Ethyl 3-[4-(6-acetoxy-7-t-butyl-2-methylchroman-2-ylmethoxy)phenyl]-2-chloropropionate (Step A4)

Following the procedure described in Preparation 51, 1.74 g of 6-acetoxy-2-(4-aminophenoxymethyl)-7-t-butyl-2-methylchroman (prepared as described in Preparation 58), 380 mg of sodium nitrite, 0.8 ml of concentrated hydrochloric acid, 4.5 g of ethyl acrylate, 65 mg of cuprous oxide and 17 ml of acetone were reacted, to give the title compound as a slightly yellow oil.

Rf value on silica gel thin layer chromatography = 0.55 (developing solvent, benzene:ethyl acetate = 5:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.23 (3H, triplet, J = 7.5Hz);

1.31 (9H, singlet);

1.45 (3H, singlet);

1.83-2.20 (2H, multiplet);

2.28 (3H, singlet);

2.72 (2H, broad triplet, J = 7Hz);

3.08 (1H, doublet of doublets, J = 7.5 & 15Hz);

3.30 (1H, doublet of doublets, J = 7.5 & 15Hz);

3.88 & 3.98 (2H, AB type, J = 9Hz);

4.18 (2H, quartet, J = 7.5Hz);

4.37 (1H, triplet, J = 7.5Hz);

6.73 (1H, singlet);

6.85 (1H, singlet);

6.88 (2H, doublet, J = 9Hz);

7.15 (2H, doublet, J = 9Hz).

PREPARATION 60

6-t-Butoxycarbonylmethoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one

A mixture of 5.6 g of sodium hydroxide, 150 ml of ethanol and 20 ml of water was added dropwise to a mixture of 25 g of 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 47), 30 ml of dimethylformamide and 150 ml of ethanol, whilst ice-cooling, and the reaction mixture was stirred for 3 hours. 18.3 g of t-butyl bromoacetate were then added. The reaction mixture was stirred for 1 hour at room temperature and then allowed to stand overnight. After this, the reaction mixture was poured into water, neutralized with a 10% w/v aqueous hydrogen chloride solution and extracted with benzene. This extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography eluted with a 20:1 by volume mixture of benzene and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.49 (developing solvent, benzene:ethyl acetate = 10:1 by volume)

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.53 (12H, singlet);

2.07 (3H, singlet);

2.27 (3H, singlet);

2.57 (3H, singlet);

2.68 (1H, doublet, J = 16.5Hz);

3.05 (1H, doublet, J = 16.5Hz);

4.17 (2H, singlet, and 2H, AB-type, J = 10Hz);

6.97 (2H, doublet, J = 9Hz);

8.19 (2H, doublet, J = 9Hz).

PREPARATION 61

6-Ethoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman

1.6 g of a 55% w/w suspension of sodium hydride in mineral oil was added to a mixture of 11 g of 6-hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman and 100 ml of dimethylformamide, and the reaction mixture was stirred for 1 hour at room temperature. The a mixture of 5.7 g of ethyl iodide and 5 ml of benzene was added dropwise, whilst ice-cooling, and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was then poured into water and extracted with benzene. This extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled from the extract under reduced pressure, and the residue was purified by silica gel column chromatography eluted with a 3:7 by volume mixture of cyclohexane and benzene, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.48 (developing solvent, benzene).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.39 (3H, triplet, J = 7Hz);

1.43 (3H, singlet);

1.7-2.1 (2H, nd);

2.06 (3H, singlet);

2.14 (3H, singlet);

2.17 (3H, singlet);

2.63 (2H, broad triplet, J = 7Hz);

3.72 (2H, quartet, J = 7Hz);

4.00 & 4.08 (2H, AB-type, J = 10Hz);

6.98 (2H, doublet, J = 9Hz);

8.17 (2H, doublet, J = 9Hz).

PREPARATION 62

2-(4-Aminophenoxymethyl)-6-t-butoxycarboxymethoxy-2,5,7,8-tetramethylchroman-4-one

A mixture of 17 g of 6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one (prepared as described in Preparation 60), 3.5 g of 10% w/w palladium-on-carbon, 150 ml of methanol and 50 ml of dimethylformamide was subjected to reduction with Paar's hydrogenation apparatus under a hydrogen pressure of 3-5 atmospheres (about 3-5 bars) for 7 hours. The palladium-on-carbon was then filtered off, and the solvent was distilled from the filtrate under reduced pressure. The residue was dissolved in benzene, washed with water and dried over anhydrous sodium sulphate.

The solvent was then distilled off under reduced pressure to give the title compound.

Rf value on silica gel thin layer chromatography = 0.29 (developing solvent, benzene:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.47 (3H, singlet);

1.54 (9H, singlet);

2.11 (3H, singlet);

2.26 (3H, singlet);

2.55-2.75 (1H, nd);

2.57 (3H, singlet);

3.05 (1H, doublet, J = 16Hz);

3.15-3.65 (2H, broad singlet);

3.90 & 4.03 (2H, AB-type, J = 10Hz);

4.17 (2H, singlet);

6.60 (2H, doublet, J = 9Hz);

6.76 (2H, doublet J = 9Hz).

PREPARATION 63

2-(4-Aminophenoxymethyl)-6-ethoxy-2,5,7,8-tetramethylchroman

The procedure described in Preparation 62 was repeated, except that 11 g of 6-ethoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman (prepared as described in Preparation 61), 2.2 g of 10% w/w palladium-on-carbon, 100 ml of methanol and 30 ml of benzene were used as the starting materials to give the title compound, melting at 121-123°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.38 (3H, triplet, J = 7Hz);

1.40 (3H, singlet);

1.7-2.1 (2H, nd);

2.08 (3H, singlet);

2.12 (3H, singlet);

2.17 (3H, singlet);

2.60 (2H, broad triplet, J = 7Hz);

3.1-3.6 (2H, broad, disappeared on adding heavy water);

3.71 (2H, quartet, J = 7Hz);

3.80 & 3.91 (2H, AB-type, J = 10Hz);

6.60 (2H, doublet, J = 9Hz);

6.78 (2H, doublet, J = 9Hz).

PREPARATION 64

Ethyl 3-[4-(6-t-Butoxycarbonylmethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate

16 ml of concentrated hydrochloric acid, 7 ml of an aqueous solution containing 3.1 g of sodium nitrite and 37 ml of ethyl acrylate were added, in that oder, at 5-10°C to a mixture of 16 g of 2-(4-aminophenoxymethyl)-6-t-butoxycarbonylmethoxy-2,5,7,8-tetramethylchroman-4-one (prepared as described in Preparation 62) and 160 ml of acetone. Then 0.5 g of cuprous oxide was added gradually at an internal temperature of 40-43°C. After about 30 minutes, the evolution of nitrogen had ceased. The reaction mixture was than poured into water and extracted with benzene. This extract was washed with water and dried over anhydrous sodium sulphate. The solvent was distilled from the extract under reduced pressure, and the residue was purified by silica gel column chromatography eluted with a 9:1 by volume mixture of cyclohexane and ethyl acetate, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.33 (developing solvent, cyclohexane:ethyl acetate = 4:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.23 (3H, triplet, J = 7.5Hz);

1.50 (3H, singlet);

1.53 (9H, singlet);

2.09 (3H, singlet);

2.26 (3H, singlet);

2.5-2.8 (1H, nd);

2.57 (3H, singlet);

3.05 (1H, doublet, J = 16Hz);

3.07 (1H, nd);

3.32 (1H, doublet of doublets, J = 7 & 14Hz);

3.98 & 4.09 (2H, AB-type, J = 10Hz);

4.05-4.35 (2H, nd);

'.18 (2H, singlet);

4.37 (1H, triplet, J = 7Hz);

6.85 (2H, doublet, J = 8Hz);

7.14 (2H, doublet, J = 8Hz).

PREPARATION 65

Ethyl 2-chloro-3-[4-(6-ethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]propionate

The procedure described in Preparation 64 was repeated, except that 9.5 g of 2-(4-aminophenoxymethyl)-6-ethoxy-2,5,7,8-tetramethylchroman (prepared as described in Preparation 63), 10 ml of concentrated hydrochloric acid, 2.4 g of sodium nitrite, 26.8 g of ethyl acrylate, 0.4 g of cuprous oxide and 100 ml of acetone were used as the starting materials, to give the title compound.

Rf value on silica gel thin layer chromatography = 0.30 (developing solvent, cyclohexane:ethyl acetate = 20:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.23 (3H, triplet, J = 7Hz);

1.38 (3H, triplet, J = 7Hz);

1.41 (3H, singlet);

1.7-2.1 (2H, nd);

2.07 (3H, singlet);

2.13 (3H, singlet);

2.17 (3H, singlet);

2.60 (2H, broad triplet, J = 7Hz);

3.07 (1H, doublet of doublets, J = 4 & 14Hz);

3.31 (1H, doublet of doublets, J = 4 & 14Hz);

3.71 (2H, quartet, J = 7Hz);

3.86 & 3.96 (2H, AB-type, J = 9Hz);

4.17 (2H, quartet, J = 7Hz);

4.38 (1H, triplet, J = 7.5Hz);

6.85 (2H, doublet, J = 9Hz);

7.13 (2H, doublet, J = 9Hz).

TEST EXAMPLE 1

Toxicity

The test animals used were male mice of the ddY strain. The animals were employed in groups of 3. The animals of each group were administered orally with a single test compound in a dose of 300 mg/kg body weight. The compounds employed were those prepared as described in Examples 3, 4, 5 and 13. The animals were then observed for one week after administration, during which time they showed no abnormalities which could be attributed to the test compounds. All animals were alive at the end of the 1 week observation period.

In view of the substantial dose administered to each animal, the zero mortality indicates that the compounds of the invention have a very low toxicity.

TEST EXAMPLE 2

Effect on Hyperglycemia

The test animals employed were genetically diabetic male mice of the KK strain, aged about 6 months. The animals were employed in groups of 3 (test compounds) or 5 (control) for each test.

The test compounds were suspended in a 0.5% w/v aqueous solution of carboxymethylcellulose. Each test compound was administered at a dose of 50 mg/kg body weight.

Within a period of about 3-24 hours after administration, blood samples were taken from the tip of the tail of each mouse, and the blood glucose level was measured in this sample by the glucose oxidase method. The minimum glucose level (i.e. maximum decrease) was taken for each animal.

A control group was treated similarly, except that the test compound was omitted.

The maximum decrease in blood glucose levels was calculated for each test compound as a percentage of the corresponding level of the control group. The results are shown in Table 29:

Table 29

Cpd. of Ex. No.	Blood glucose level (%)
Control	100
13	61.5
58	67.5
59	53.4

TEST EXAMPLE 3

Effect on Aldose Reductase

Aldose reductase was separated and partially purified from bovine lenses by the method of Hayman and Kinoshita [J. Biol. Chem., 240, 877 - (1965)]. Enzyme activities were photometrically determined by the method of Varma et al . [Biochem, Pharmac., 25, 2505 (1976)].

The inhibition of aldose reductase activity was determined employing each test compound in a concentration of 1 x 10^{-5} M, and the results are as shown in Table 30.

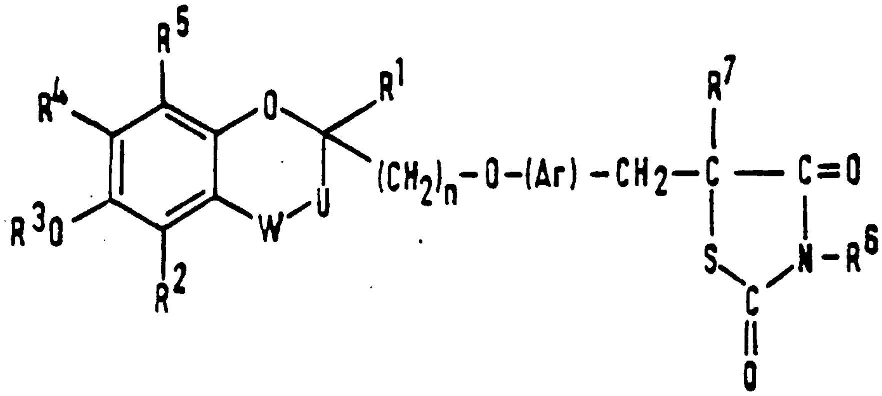
As a control, the known compound, 5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione ("Cpd. A") was tested by the same method and the result is also shown in Table 30:

Table 30

Cpd. of Ex. No.	Percent Inhibition
13	55.5
58	51.6
59	79.5
Cpd. A	16.2

Claims

1. Compounds of formula (I):



(I)

in which:

R^1 represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_7-C_{13} aralkyl group;

R^2 represents a hydrogen atom or a C_1-C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1-C_{22} alkanoyl group, a C_3-C_{22} alkenoyl group, a C_3-C_{22} alkynoyl group, a substituted C_1-C_{22} alkanoyl, C_3-C_{22} alkenoyl or C_3-C_{22} alkynoyl group having at least one of substituents (a), an aromatic acyl group, a heterocyclic acyl group, a group of formula $-SO_3R^8$ where

R^8 represents a hydrogen atom, an aralkyl group where the alkyl part is C_1-C_3 alkyl, a C_1-C_5 alkyl group or a C_1-C_5 alkyl group having at least one hydroxy or C_1-C_5 substituent,

a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one of substituents (b);

R^4 represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_1-C_5 alkoxy group;

R^5 represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group;

R^6 and R^7 are the same or different and each represents a hydrogen atom, a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one of substituents (b);

Ar is a divalent carbocyclic aromatic group or a divalent heterocyclic aromatic groups;

W represents a $-CH_2$-group, a >C=O group, a group of formula >CH-OR^{11}

wherein R^{11} represents a hydrogen atom, a C_1-C_{22} alkanoyl group, a C_3-C_{22} alkenoyl group, a C_3-C_{22} alkynoyl group, a substituted C_1-C_{22} alkanoyl, C_3-C_{22} alkenoyl or C_3-C_{22} alkynoyl group having at least one of substituents (a), an aromatic acyl group, a heterocyclic acyl group, a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one of substituents (b),

or a group of formula >C=N-O-R^{12}.

in which R^{12} represents a hydrogen atom, a C_1-C_{10} alkyl group, a C_1-C_{10} alkyl group having at least one of substituents (b), a C_1-C_{22} alkanoyl group, a C_3-C_{22} alkenoyl group, a C_3-C_{22} alkynoyl group, a substituted C_1-C_{22} alkanoyl, C_3-C_{22} alkenoyl or C_3-C_{22} alkynoyl group having at least one of substituents - (a), an aromatic acyl group, a heterocyclic acyl group or a group of formula $-CONR^9R^{10}$ where

R^9 and R^{10} are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group or R^9 and R^{10}, together with the nitrogen atom to which they are attached, represent a heterocyclic group having from 5 to 7 ring atoms of which from 1 to 3 atoms, including said nitrogen atom, are nitrogen, oxygen or sulphur hetero-atoms, said heterocyclic group being unsubstituted, or, where said ring atoms include an additional nitrogen hetero-atom, said additional nitrogen atom being unsubstituted or having a single substituent se-

lected from substituents (e);

U represents a $-CH_2-$group;

or

W and U together represent a group of formula $-CH=CH-$;

or

when W represents a carbonyl group or said group of formula $>C=N-OR^{12}$, U, R^1 and the carbon atom to which R^1 is attached together represent a group of formula $-CH=C<$;

n is an integer of from 1 to 3;

said aryl groups and the aryl parts of said aralkyl, aralkyloxycarbonyl, aromatic acyl, aromatic acyloxy and divalent aromatic groups being C_6-C_{10} carbocyclic aryl groups which are unsubstituted or have at least one of substituents (c);

said heterocyclic groups, heterocyclic parts of said heterocyclic acyl and acyloxy groups and said divalent heterocyclic aromatic groups have from 5 to 10 ring atoms, of which from 1 to 5 are nitrogen, oxygen or sulphur hetero-atoms, said heterocyclic groups being unsubstituted or having at least one of substituents (d);

said substituents (a) being aryl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups or aralkyloxycarbonyl groups;

said substituents (b) being hydroxy groups, C_1-C_6 alkoxy groups, aryl groups, C_1-C_{22} alkanoyloxy groups, C_3-C_{22} alkenoyloxy groups, C_3-C_{22} alkynoyloxy groups, substituted C_1-C_{22} alkanoyloxy, C_3-C_{22} alkenoyloxy or C_3-C_{22} alkynoyloxy groups having at least one of substituents (a), aromatic acyloxy groups, heterocyclic acyloxy groups, groups of formula $-COOR^8$ where R^8 is as defined above and groups of formula $-CONR^9R^{10}$ where R^9 and R^{10} are as defined above;

said substituents (c) being C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups, C_1-C_6 alkyl groups having at least one halogen substituent, halogen atoms, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups in which each alkyl part is C_1-C_6, nitro groups, cyano groups, groups of formula $-CONR_2$ - (where R represents a C_1-C_6 alkyl group or an aryl group) or hydroxy groups;

said substituents (d) being C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups or doubly bonded oxygen atoms;

and

said substituents (e) being C_1-C_6 alkyl groups, C_1-C_6 alkanoyl groups, C_3-C_6 alkenoyl groups or C_3-C_6 alkynoyl groups;

provided that:

(α) where: R^3 represents said hydrogen atom, an unsubstituted C_1-C_6 alkanoyl group, an unsubstituted C_3-C_6 alkenoyl group, an unsubstituted C_3-C_6 alkynoyl group, said aromatic acyl group, said heterocyclic acyl group, an aralkanoyl group or an aralkenoyl group; and R^6 and R^7 both represent hydrogen atoms; and Ar represents a p-phenylene group; and W represents a group of formula $>CH_2$, $>C=O$ or $>CH-OR^{11x}$ (wherein R^{11x} represents a hydrogen atom, an unsubstituted C_1-C_6 alkanoyl group, an unsubstituted C_3-C_6 alkenoyl group, an unsubstituted C_3-C_6 alkynoyl group, said aromatic acyl group, said heterocyclic acyl group, an aralkanoyl group or an aralkenoyl group); and U represents said group of formula $>CH_2$,

then

(i) when R^1 represents a hydrogen atom or a C_1-C_5 alkyl group, R^4 represents a C_6-C_{10} alkyl group, and

(ii) when R^4 represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, R^1 represents a C_6-C_{10} alkyl group or said C_7-C_{13} aralkyl group; or

(β) where: R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group; and R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group; and Ar represents a p-phenylene group; and W is a group of formula $>CH_2$, $>C=O$ or $>CH-OR^{11x}$ (where R^{11x} is as defined above); and U represents said group of formula $>CH_2$;

and n is an integer from 1 to 3,

then

at least one of R^3, R^6 and R^7 represents said alkyl or substituted alkyl group;

and pharmaceutically acceptable salts thereof.

2. Compounds as claimed in Claim 1, in which:

R^1 represents a hydrogen atom or a C_1-C_{10} alkyl group;

R^2 represents a hydrogen atom or a C_1-C_3 alkyl group;

R^3 represents a hydrogen atom, a sulpho group, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one of substituents (g), a group of formula R^{13}-$(CH_2)_m$-CO-, where

R^{13} represents a phenyl group or a phenyl group having at least one of substituents (g), and m is an integer from 1 to 5,

a group of formula Het-CO-, where

Het represents a heterocyclic group having 5 or 6 ring atoms, of which from 1 to 3 are nitrogen, oxygen or sulphur hetero-atoms, said heterocyclic group being unsubstituted or having at least one C_1-C_5 alkyl substituent,

a C_1-C_5 alkyl group, a C_1-C_5 alkyl group substituted by a group of formula -$COOR^{8a}$, where

R^{8a} represents a hydrogen atom, a C_1-C_5 alkyl group or an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_5,

a C_2-C_5 hydroxyalkyl group, an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_5, a C_2-C_5 alkyl group substituted by a group of formula -O-CO-R^{53}, where

R^{53} represents a C_1-C_{10} alkyl group, a phenyl group, a phenyl group having at least one of substituents (g) or a heterocyclic group Het, as defined above,

or a C_1-C_3 alkyl group substituted by a single substituent selected from substituents (h);

said substituents (f) being phenyl groups, carboxy groups, C_2-C_6 alkoxycarbonyl groups or benzyloxycarbonyl groups;

said substituents (g) being C_1-C_5 alkyl groups, trifluoromethyl groups, C_1-C_5 alkoxy groups, halogen atoms, nitro groups, amino groups, hydroxy groups or dialkylamino groups where each alkyl part is C_1-C_5;

said substituents (h) being alkylcarbamoyl groups where the alkyl part is C_1-C_4, dialkylcarbamoyl groups where each alkyl part is C_1-C_4, 1-pyrrolidinylcarbonyl groups, piperidinocarbonyl groups or morpholinocarbonyl groups;

R^4 represents a C_1-C_{10} alkyl group or a methoxy group;

R^5 represents a hydrogen atom, a C_1-C_5 alkyl group or a methoxy group;

R^6 and R^7 the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group, a C_1-C_5 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined above, a C_2-C_5 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a group of formula -O-CO-R^{53} (where R^{53} is as defined above), or a C_1-C_3 alkyl group having a single substituent selected from substituents (h);

Ar represents a o-phenylene, m -phenylene or p-phenylene group or a pyridine-diyl group which is attached to the part of said compound of formula (I) of formula -$(CH_2)_n$-O-at its 2-position and is attached to the -CH_2-thiazolidine group at its 5-or 6-position, said phenylene and pyridine-diyl groups being unsubstituted or having a C_1-C_3 alkyl substituent;

W represents a group of formula -CH_2-, >C=O >CH-OR^{11} or > C=N-OR^{12} where

R^{11} represents a hydrogen atom, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one substituents (g), a group of formula R^{13}-$(CH_2)_m$-CO- where R^{13} and m are as defined above or a group of formula Het-CO-where Het is as defined above, and

R^{12} represents a hydrogen atom, a C_1-C_5 alkyl group, a C_1-C_{10} alkyl group having at least one of substituents (j), a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one of substituents (g), or said group of formula R^{13}-$(CH_2)_m$-CO-or Het-CO-; and

said substituents (j) being hydroxy groups, C_1-C_5 alkoxy groups, phenyl groups, phenyl groups having at least one of substituents (g), C_2-C_{11} alkanoyloxy groups, C_2-C_{11} alkanoyloxy groups substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined above, C_3-C_{11} alkenoyloxy groups substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined above, phenylalkenoyloxy groups where the alkenyl part is C_2-C_{10} and the phenyl part is unsubstituted or has at least one of substituents (g), benzoyloxy groups, benzoyloxy groups having

at least one of substituents (g), groups of formula -$COOR^{8a}$ where. R^{8a} is as defined above, benzyloxycarbonyl groups and groups of formula -$COR^{9}R^{10}$ where R^{9} and R^{10} are as defined above; U represents

(i) where W represents a group of formula -CH_2-. >C = O, >CH_2OR^{11} or >C = N-OR^{12}, a group of formula -CH_2-.

(ii) with W, a group of formula -CH = CH-. or

(iii) where W represents a group of formula >C = O or >C = N-OR^{14}, in which R^{14} represents any one of the acyl groups defined for R^{12}, with R^1 and the carbon atom to which R^1 is attached, a group of formula -CH = C<.

3. Compounds as claimed in Claim 2, in which:

R^1,R^2,R^4,R^5, Ar, W and U are as defined in Claim 2;

R^6 and R^7 both represent hydrogen atoms;

R^3 and R^{11} are the same or different and each represents a hydrogen atom, C_1-C_{20} alkanoyl group, a C_3-C_{20} alkenoyl group, a C_1-C_{20} alkanoyl or C_3-C_{20} alkenoyl group having at least one of substituents -(f) as defined in Claim 2, an arylcarbonyl group as defined in Claim 2, or a group of formula R^{13} -$(CH_2)_m$-CO-or Het-CO-where R^{13}, m and Het are as defined in Claim 2; and

R^{12} represents any one of the groups or atoms defined for R^3 and R^{11} or a C_1-C_6 alkyl group or a C_1-C_3 alkyl group having at least one of substituents (f) as defined in Claim 2.

4. Compounds as claimed in Claim 2, in which;

R^1,R^2,R^4,R^5, Ar, W and U are as defined in Claim 2;

R^3,R^6,R^7 and R^{12} are the same or different and each represents a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2, a C_2-C_6 hydroxyalkyl group, a C_1-C_6 alkyl group substituted by a C_1-C_6 alkoxy group, a C_2-C_6 alkyl group substituted by a group of formula -O-CO-R^{8b} where R^{8b} is as defined in Claim 2 or a C_1-C_3 alkyl group substituted by a single substituent selected from substituents (h) as defined in Claim 2; and

R^{11} represents a hydrogen atom, an acetyl group or a benzoyl group;

or

R^{12} represents a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_{10} alkyl group having at least one of substituents (k), a C_2-C_6 alkanoyl group, a C_2-C_{10} alkanoyl group having at least one of substituents -(l), a C_3-C_6 alkenoyl group, a C_3-C_6 alkenoyl group having at least one of substituents (l), a benzoyl group, a benzoyl group having at least one of substituents (m), a pyridinecarbonyl group, a furoyl group, a thenoyl group or a pyridinecarbonyl, furoyl or thenoyl group having at least one C_1-C_6 alkyl substituent;

said substituents (k) being hydroxy groups, phenyl groups, phenyl groups having at least one of substituents (m), C_2-C_6 alkanoyloxy groups, C_2-C_{10} alkanoyloxy or C_3-C_{10} alkenoyloxy groups substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2, C_3-C_{10} alkenoyloxy groups substituted by a phenyl group where the phenyl group is unsubstituted or has at least one of substituents (m), benzoyloxy groups, benzoyloxy groups having at least one of substituents (m), groups of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2 or substituents (h) as defined in Claim 2;

said substituents (l) being phenyl groups, carboxy groups, alkoxycarbonyl groups where the alkoxy part is C_1-C_6 or benzyloxycarbonyl groups; and

said substituents (m) being C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups, halogen atoms or trifluoromethyl groups.

5. Compounds as claimed in Claim 1, in which;

R^1 represents a methyl, ethyl, isobutyl, pentyl, hexyl, 3,3-dimethylbutyl, heptyl, 4,4-dimethylpentyl, octyl, 5,5-dimethylhexyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_{10} alkanoyl Group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f), a benzoyl group, a benzoyl group having at least one of substituents (n), an aralkanoyl group of formula R^{15}-$(CH_2)_m$-CO-

where R^{15} represents a phenyl group or a phenyl group having at least one of substituents (n), and m is an integer from 1 to 5,

a pyridinecarbonyl group, a furoyl group, a thenoyl group, a C_1-C_3 alkyl group, a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where

R^{8a} represents a hydrogen atom, a C_1-C_6 alkyl group or an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_4,

a C_2-C_3 hydroxyalkyl group, a C_1-C_6 alkyl group substituted by a C_1-C_6 alkoxy group, a C_2-C_6 alkyl

group substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group or a methyl group having a single substituent selected from substituents (h);

said substituents (f) being phenyl groups, carboxy groups, C_2-C_6 alkoxycarbonyl groups or benzyloxycarbonyl groups;

said substituents (n) being C_1-C_5 alkyl groups,

C_1-C_5 alkoxy groups or halogen atoms;

R^4 represents a C_1-C_{10} alkyl group;

R^5 represents a hydrogen atom or a C_1-C_3 alkyl group;

R^6 and R^7 are the same or different and each represents a hydrogen atom, a C_1-C_3 alkyl group, a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined above, a C_2-C_3 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group, or a methyl group substituted by a single substituent selected from substituents (h);

said substituents (h) being alkylcarbamoyl groups where the alkyl part is C_1-C_4, dialkylcarbamoyl groups where each alkyl part is C_1-C_4, 1-pyrrolidinylcarbonyl groups, piperidinocarbonyl groups or morpholinocarbonyl groups;

Ar represents a o-phenylene, m-phenylene or p-phenylene group or a pyridine-diyl group which is attached to the part of said compound of formula -(I) of formula -$(CH_2)_n$-O-at its 2-position and is attached to the -CH_2-thiazolidine group at its 5-or 6-position, said phenylene and pyridine-diyl groups being unsubstituted or having a methyl substituent;

W represents a group of formula -CH_2-, >C=O, >CH-OR^{11} or >C=N-OR^{12}, where:

R^{11} represents a hydrogen atom or any one of the acyl groups defined above for R^3; and

R^{12} represents a benzyl group, any one of the groups or atoms defined above for R^3, a pyridinecarbonyl group or a pyridinecarbonyl group having at least one C_1-C_5 alkyl substituent; and U represents

(i) where W represents a group of formula -CH_2-, >C=O, >CH-OR^{11} or > C=N-OR^{12}, a group of formula -CH_2-,

(ii) with W, a group of formula -CH=CH-, or

(iii) wher W represents a group of formula > C=O with R^1 and the carbon atom to which R^1 is attached, a group of formula -CH=C<.

6. Compounds as claimed in Claim 5, in which:

R^1,R^2,R^4,R^5, Ar, W and U are as defined in Claim 5;

R^6 and R^7 are both hydrogen atoms;

R^3 and R^{11} are the same or different and each represents a hydrogen atom, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f) as defined in Claim 5, a benzoyl group, a benzoyl group having at least one of substituents (n) as defined in Claim 5, a group of formula R^{15}-$(CH_2)_m$-CO-(where R^{15} and m are as defined in Claim 5), a pyridinecarbonyl group, a furoyl group or a thenoyl group; and

R^{12} represents a hydrogen atom, a methyl group, a benzyl group, a t-butoxycarbonylmethyl group or any one of the acyl groups defined above for R^3 and R^{11}.

7. Compounds as claimed in Claim 5, in which::

R^1,R^2,R^4,R^5, Ar, W and U are as defined in Claim 5;

R^3,R^6 and R^7 are the same or different and each represents a C_1-C_3 alkyl group, a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 5, a C_2-C_3 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group, or a methyl group having a single substituent selected from substituents (h) as defined in Claim 5;

R^{11} represents a hydrogen atom;

R^{12} represents a hydrogen atom, a C_1-C_3 alkyl group having at least one of substituents (o), a C_2-C_4 alkanoyl group, a C_2-C_4 alkanoyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 5, an acryloyl group, an acryloyl group having a β-substituent selected from substituents (f), a benzoyl group, a benzoyl group having at least one of substituents (q), a pyridinecarbonyl group, a pyridinecarbonyl group having at least one C_1-C_5 alkyl substituent or any one of the groups defined above for R^3, R^6 and R^7;

said substituents (f) being phenyl groups, carboxy groups, C_2-C_6 alkoxycarbonyl groups or benzyloxycarbonyl groups;

said substituents (o) being carboxy groups or al-

koxycarbonyl groups where the alkoxy part is C_1-C_4; and

said substituents (q) being methyl groups, ethyl groups, methoxy groups or ethoxy groups.

8. Compounds as claimed in Claim 1 in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_6 alkanoyl group, C_3-C_6 alkenoyl group, a cinnomoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-

where R^{16} represents a hydrogen atom or a C_1-C_4 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula $R^{17}OOC.CH=CH$-CO-

where R^{17} represents a hydrogen atom, a C_1-C_4 alkyl group or a benzyl group,

a 2-, 3-or 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula $-COOR^{8a}$ where

R^{8a} represents a hydrogen atom, a C_1-C_4 alkyl group or an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_4;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are the same or different and each represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined above;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula $-(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula $-(CH_2)_n$ -O-at the 2-position and to the $-CH_2$-thiazolidine group at the 5-position;

W represents a group of formula $-CH_2$-, > C=O, >C=N-OH, >C=N-OCH_2COOH or >C=N-$OCOR^{18}$

where R^{18} represents a C_1-C_4 alkyl group; and

U represents a group of formula $-CH_2$-.

9. Compounds as claimed in Claim 8, in which:

R^1, R^2, R^4, R^5, Ar and U are as defined in Claim 8;

R^3 represents a hydrogen atom, a C_1-C_6 alkanoyl group, a C_3-C_6 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-where R^{16} and m are as defined in Claim 8, a cis or trans-group of formula $R^{17}OOC.CH=CH$-CO-where R^{17} is as defined in Claim 8, or a 2-, 3-or 4-pyridinecarbonyl group;

R^6 and R^7 are both hydrogen atoms;

W represents a group of formula >C=NOR^{12} where

R^{12} represents a hydrogen atom, a group of formula $-CH_2)_2COOR^{8a}$, $-CH_2COOR^{8a}$, $-C(CH_3)_2COOR^{8a}$, -$COCH_2CH_2COOR^{8a}$ or -CO-CH=CH-$COOR^{8a}$ where R^{8a} is as defined in Claim 8, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group or any one of the groups defined above for R^3, R^6 and R^7; and

n is 1 or 2.

10. Compounds as claimed in Claim 8, in which:

R^1, R^2, R^4, R^5, Ar and U are as defined in Claim 8;

R^3, R^6 and R^7 are the same or different and each represents a C_1-C_3 alkyl group substituted by a group of formula $-COOR^{8a}$ where R^{8a} is as defined in Claim 8;

W represents a group of formula >CH_2, >C=O or >C=NOR^{12};

R^{12} represents a hydrogen atom, a group of formula $-(CH_2)_2COOR^{8a}$, $-CH_2COOR^{8a}$, $-C(CH_3)_2COOR^{8a}$, -$COCH_2CH_2COOR^{8a}$ or -CO-CH=CH-$COOR^{8a}$ where R^{8a} is as defined in Claim 8, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group or any one of the groups defined above for R^3,R^6 and R^7;

and

n is 1 or 2.

11. Compounds as claimed in Claim 2, in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_{18} alkanoyl

group, a C_3-C_{10} alkenoyl group, a C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f) as defined in Claim 2, an arylcarbonyl group as defined in Claim 2, a group of formula R^{13}-$(CH_2)_m$-CO-or Het-CO-where R^{13}, m and Het are as defined in Claim 2 or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 represents a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2;

R^7 represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula >CH_2, >C=O or >C=NOR^{12}, where

R^{12} represents a hydrogen atom, a group of formula -$(CH_2)_2COOR^{8a}$, -CH_2COOR^{8a}, -$C(CH_3)_2COOR^{8a}$, -$COCH_2CH_2COOR^{8a}$ or -CO-CH=CH-$COOR^{8a}$ where R^{8a} is as defined in Claim 2, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2;

U represents a group of formula -CH_2-; and

n is 1 or 2.

12. Compounds as claimed in Claim 2, in which:

R^1 represents a hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_5 alkanoyl group, C_3-C_5 alkenoyl group, a cinnamoyl group, a group of formula $R^{15}OOC(CH_2)_mCO$-

where R^{15} represents a hydrogen atom or a C_1-C_5 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula R^{17}OOC.CH=CH-CO-

where R^{17} represents a hydrogen atom, C_1-C_5 alkyl group or a benzyl group,

a 2-, 3-or 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are the same or different and each represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 2;

Ar represents ap-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula -CH_2-, >C=O or >C=N-OR^{12}, where

R^{12} represents a hydrogen atom, a group of formula -$(CH_2)_2COOR^{8a}$, -CH_2COOR^{8a}, -$C(CH_3)_2COOR^{8a}$, -$COCH_2CH_2COOR^{8a}$ or -CO-CH=CH-$COOR^{8a}$ where R^{8a} is as defined in Claim 2, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group, a C_1-C_5 alkyl group, a C_1-C_5 alkyl group substituted by a phenyl group where the phenyl group is unsubstituted or has at least one of substituents (n), or any one of the groups defined above for R^3, R^6 and R^7;

said substituents (n) being C_1-C_5 alkyl groups, C_1-C_5 alkoxy groups or halogen atoms; and

U represents a group of formula -CH_2-.

13. Compounds as claimed in Claim 2, in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_5 alkanoyl group, C_3-C_5 alkenoyl group, a cinnamoyl group, a

group of formula $R^{16}OOC(CH_2)_mCO$-

where R^{16} represents a hydrogen atom or a C_1-C_6 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula $R^{17}OOC.CH=CH$-CO-

where R^{17} represents a hydrogen atom, a C_1-C_6 alkyl group or a benzyl group,

a 2-, 3-or 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{9a}$ where R^{9a} is as defined in Claim 2;

R^4 represents a hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are the same or different and each represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{9a}$ where R^{9a} is as defined in Claim 2;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula -CH_2-, >C=O or >C=N-OR^{12} where

R^{12} represents a hydrogen atom, a group of formula -$(CH_2)_2COOR^{9a}$, -CH_2COOR^{9a}, -$C(CH_3)_2COOR^{9a}$, -$COCH_2CH_2COOR^{9a}$ or -CO-CH=CH-$COOR^{9a}$ where R^{9a} is as defined in Claim 2, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group, a C_1-C_6 alkyl group, a C_1-C_6 alkyl group substituted by a phenyl group where the phenyl group is unsubstituted or has at least one of substituents (n), or any one of the groups defined above for R^3, R^6 and R^7;

said substituents (n) being C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups or halogen atoms; and

U represents a group of formula -CH_2-.

14. Compounds as claimed in Claim 2, in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents C_1-C_3 alkyl group substituted by a group of formula -$COOR^{9a}$, where R^{9a} is as defined in Claim 2;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are both hydrogen atoms;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$ -O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula -CH_2-, >C=O, >C=N-OH, or >C=N-O-(C_1-C_3 alkyl)-$COOR^{9a}$ where R^{9a} is as defined in Claim 2;

U represents a group of formula -CH_2-; and

n is 1 or 2.

15. Compounds as claimed in Claim 2, in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a group of formula -CH_2-$COOR^{9a}$ where R^{9a} is as defined in Claim 2;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are both hydrogen atoms;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$ -O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula -CH_2-, >C=O, >C=N-OH, or > C=N-O-(C_1-C_3 alkyl)-$COOR^{9a}$

where R^{8a} is as defined in Claim 2;

U represents a group of formula $-CH_2-$; and

n is 1 or 2.

16. 5-[4-(6-Hydroxy-5,7,8-trimethyl-2-octylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

17. 5-{4-[6-Hydroxy-4-(E)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

18. 5-{4-[6-Acetoxy-4-(E)-acetoxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

19. α-{5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid and pharmaceutically acceptable salts thereof.

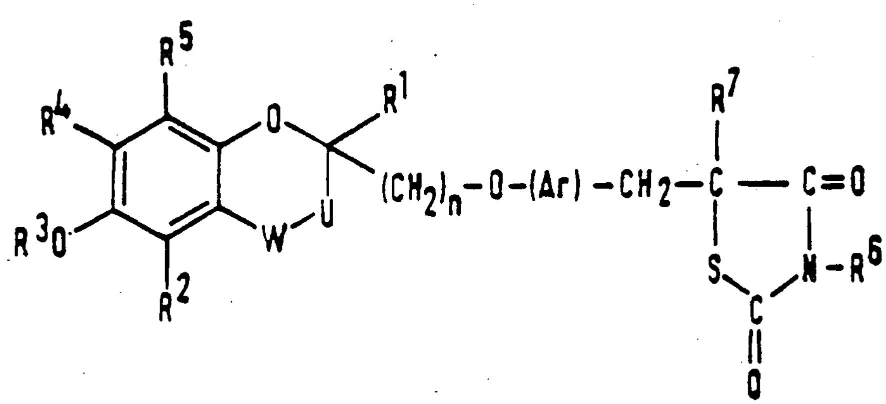
20. α-{5-[4-(6-Carboxymethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid and pharmaceutically acceptable salts thereof.

21. α,α'-{5-[4-(6-Carboxymethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)-benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetic acid and pharmaceutically acceptable salts thereof.

22. A pharmaceutical composition for the treatment of blood disorders, comprising an active compound in admixture with a pharmaceutically acceptable carrier or diluent, wherein the active compound is at least one compound as claimed in any one of Claims 1 to 21.

23. The use for the manufacture of a medicament for the treatment of blood disorders of a compound as claimed in any one of Claims 1 to 21.

24. A process for preparing compounds of formula (I):



(I)

[in which:

R^1 represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_7-C_{13} aralkyl group;

R^2 represents a hydrogen atom or a C_1-C_6 alkyl group;

R^3 represents a hydrogen atom, a C_1-C_{22} alkanoyl group, a C_3-C_{22} alkenoyl group, a C_3-C_{22} alkynoyl group, a substituted C_1-C_{22} alkanoyl, C_3-C_{22} alkenoyl or C_3-C_{22} alkynoyl group having at least one of substituents (a), an aromatic acyl group, a heterocyclic acyl group, a group of formula $-SO_3R^8$ where

R^8 represents a hydrogen atom, an aralkyl group where the alkyl part is C_1-C_3 alkyl, a C_1-C_6 alkyl group or a C_1-C_6 alkyl group having at least one hydroxy or C_1-C_6 alkoxy substitu nt,

a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one of substituents (b);

R^4 represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_1-C_6 alkoxy group;

R^5 represents a hydrogen atom, a C_1-C_6 alkyl group or a C_1-C_6 alkoxy group;

R^6 and R^7 are the same or different and each represents a hydrogen atom, a C_1-C_{10} alkyl groups or a substituted C_1-C_{10} alkyl group having at least one of substituents (b);

Ar is a divalent carbocyclic aromatic group or a divalent heterocyclic aromatic group;

W represents a $-CH_2$-group, a $>C=O$ group, a group of formula $>CH-OR^{11}$

wherein R^{11} represents a hydrogen atom, a C_1-C_{23} alkanoyl group, a C_3-C_{23} alkenoyl group, a C_3-C_{23} alkynoyl group, a substituted C_1-C_{23} alkanoyl, C_3-C_{23} alkenoyl or C_3-C_{23} alkynoyl group having at least one of substituents (a), an aromatic acyl group, a heterocyclic acyl group, a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one of substituents (b),

or a group of formula $>C=N-O-R^{12}$

in which R^{12} represents a hydrogen atom, a C_1-C_{10} alkyl group, a C_1-C_{10} alkyl group having at least one of substituents (b), a C_1-C_{23} alkanoyl group, a C_3-C_{23} alkenoyl group, a C_3-C_{23} alkynoyl group, a substituted C_1-C_{23} alkanoyl, C_3-C_{23} alkenoyl or C_3-C_{23} alkynoyl group having at least one of substituents - (a), an aromatic acyl group, a heterocyclic acyl group or a group of formula $-CONR^9R^{10}$ where

R^9 and R^{10} are the same or different and each represents a hydrogen atom or a C_1-C_4 alkyl group or R^9 and R^{10}, together with the nitrogen atom to which they are attached, represent a heterocyclic group having from 5 to 7 ring atoms of which from 1 to 3 atoms, including said nitrogen atom, are nitrogen, oxygen or sulphur hetero-atoms, said heterocyclic group being unsubstituted, or, where said ring atoms include an additional nitrogen hetero-atom, said additional nitrogen atom being unsubstituted or having a single substituent selected from substituents (e);

U represents a $-CH_2$-group;

or

W and U together represent a group of formula $-CH=CH-$;

or

when W represents a carbonyl group or said group of formula $>C=N-OR^{12}$, U, R^1 and the carbon atom to which R^1 is attached together represent a group of formula $-CH=C<$;

n is an integer of from 1 to 3;

said aryl groups and the aryl parts of said aralkyl, aralkyloxycarbonyl, aromatic acyl, aromatic acyloxy and divalent aromatic groups being C_6-C_{10} carbocyclic aryl groups which are unsubstituted or have at least one of substituents (c);

said heterocyclic groups, heterocyclic parts of said heterocyclic acyl and acyloxy groups and said divalent heterocyclic aromatic groups have from 5 to 10 ring atoms, of which from 1 to 5 are nitrogen, oxygen or sulphur hetero-atoms, said heterocyclic groups being unsubstituted or having at least one of substituents (d);

said substituents (a) being aryl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups or aralkyloxycarbonyl groups;

said substituents (b) being hydroxy groups, C_1-C_4 alkoxy groups, aryl groups, C_1-C_{23} alkanoyloxy groups, C_3-C_{23} alkenoyloxy groups, C_3-C_{23} alkynoyloxy groups, substituted C_1-C_{23} alkanoyloxy, C_3-C_{23} alkenoyloxy or C_3-C_{23} alkynoyloxy groups having at least one of substituents (a), aromatic acyloxy groups, heterocyclic acyloxy groups, groups of formula $-COOR^8$ where R^8 is as defined above or groups of formula $-CONR^9R^{10}$ where R^9 and R^{10} are as defined above;

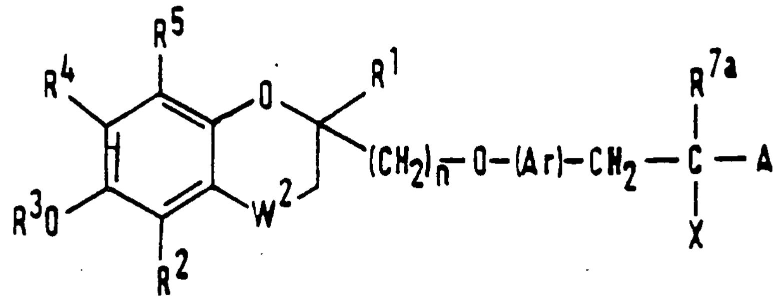
said substituents (c) being C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups, C_1-C_4 alkyl groups having at least one halogen substituent, halogen atoms, amino groups, C_1-C_4 alkylamino groups, dialkylamino groups in which each alkyl part is C_1-C_4, nitro groups, cyano groups, groups of formula $-CONR_2$ where R represents a C_1-C_4 alkyl group or an aryl group or hydroxy groups;

said substituents (d) being C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or doubly bonded oxygen atoms; and

said substituents (e) being C_1-C_4 alkyl groups, C_1-C_4 alkanoyl groups, C_3-C_4 alkenoyl groups or C_3-C_4 alkynoyl groups;]

and pharmaceutically acceptable salts thereof, which comprises the steps:

(a) reacting a compound of formula (II):



(II)

(wherein:

R^1, R^2, R^3, R^4, R^5, n and Ar are as defined above;

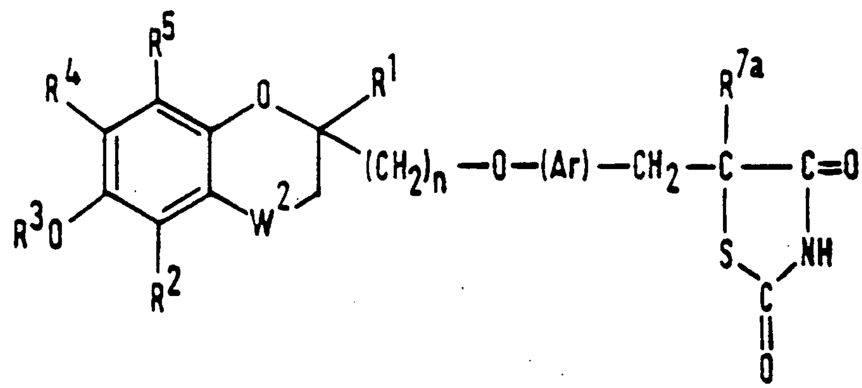
R^{7a} represents a hydrogen atom or an unsubstituted C_1-C_{10} alkyl group;

W^2 represents a methylene group or a carbonyl group;

A represents a cyano group, a carboxy group, a C_2-C_6 alkoxycarbonyl group, a carbamoyl group or a group of formula -COOM where M represents a caution; and

X represents a halogen atom)

with thiourea and hydrolysing the product to give a compound of formula (IV):



(IV)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n, Ar and W^2 are as defined above);

(b) if necessary, converting W^2 to another group represented by W or the methylene group at the 3-chroman position to another group represented by U;

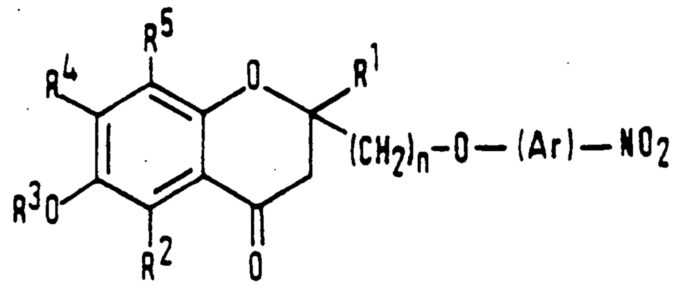
(c) if necessary, converting R^{7a} and/or the hydrogen atom at the 3-thiazolidine position to other groups represented by R^7 and R^6 respectively;

(d) if necessary, acylating and/or hydrolising the group $-OR^3$; and

(e) if necessary, salifying the product.

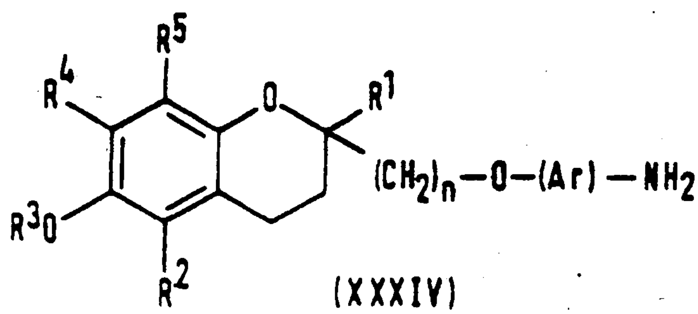
25. A process as claimed in Claim 24, wherein said compound of formula (II) is prepared by:

(i) in any order, subjecting a compound of formula (XLIX):



(XLIX)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 24) to the steps: reduction of the oxo group at the chroman-4 position to a hydroxy group, removing that hydroxy group and a 3-hydrogen atom to give a corresponding 2 H-chromene compound and hydrogenating the chromene double bond; and reducing the nitro group to an amino group, thereby giving a compound of formula (XXXIV):



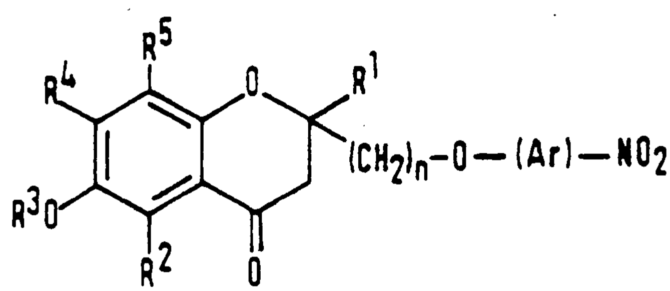
(XXXIV)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 24); and

(ii) diazotizing said compound of formula (XXXIV) and subjecting the diazotized compound to a Meerwein arylation reaction with a compound of formula $CH_2=CR^{7a}A$ (where R^{7a} and A are as defined in Claim 24) to give said compound of formula (II).

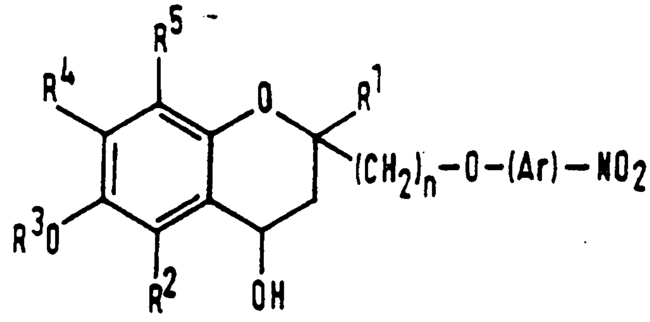
26. A process as claimed in Claim 24, which comprises the steps:

(i) reducing a compound of formula (XLIX):



(XLIX)

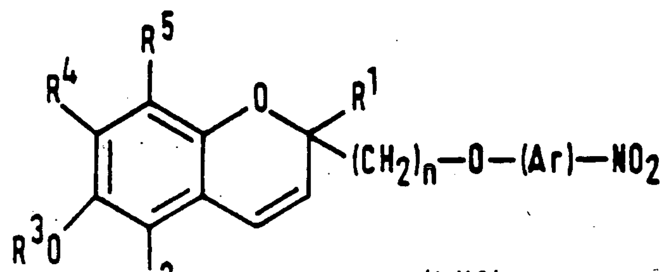
(in which R^1, R^2, R^3, R^4, R^5, n and Ar ar as defined in Claim 24) to give a compound of formula (LIX):



(LIX)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 24);

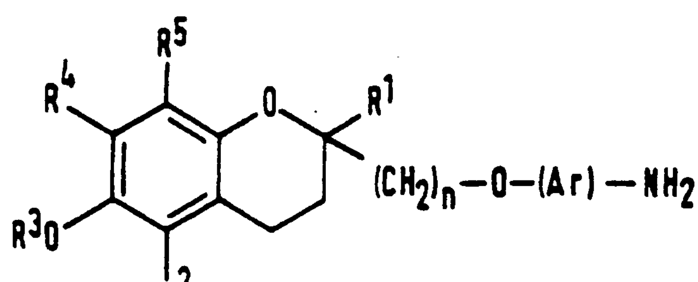
(ii) dehydrating said compound of formula - (LIX), to give a compound of formula (LXI):



(LXI)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 24);

(iii) hydrogenating said compound of formula - (LXI), to give a compound of formula (XXXIV):



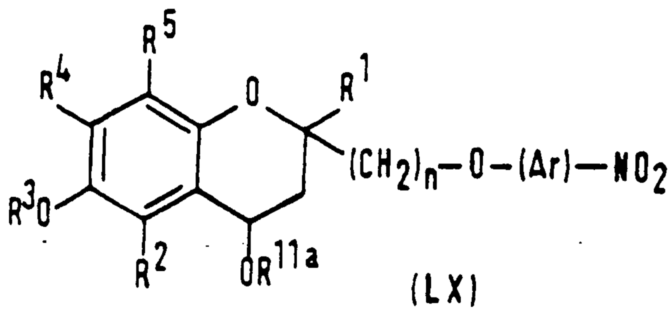
(XXXIV)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 24); and

(iv) subjecting said compound of formula (XXXIV) to step (a) and, if necessary, steps (b) to - (e) as defined in Claim 24.

27. A process as claimed in Claim 26, wherein the dehydration of step (ii) is effected by

(ii-a) acylating said compound of formula (LIX), to give a compound of formula (LX):



(LX)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 24 and R^{11a} represents an acyl group); and

(ii-b) eliminating an acid of formula R^{11a}-OH from said compound of formula (LX), to give said compound of formula (LXI).

28. A process according to any one of Claims 24 to 27, in which:

where: R^3 represents said hydrogen atom, an unsubstituted C_1-C_6 alkanoyl group, an unsubstituted C_3-C_6 alkenoyl group, an unsubstituted C_3-C_6 alkynoyl group, said aromatic acyl group, said heterocyclic acyl group, an aralkanoyl group or an aralkenoyl group: and R^6 and R^7 both represent hydrogen atoms; and Ar represents a p-phenylene group; and W represents a group of formula >CH_2, >C=O or >CH-OR^{11x} (wherein R^{11x} represents a hydrogen atom, an unsubstituted C_1-C_6 alkanoyl group, an unsubstituted C_3-C_6 alkenoyl group, an unsubstituted C_3-C_6 alkynoyl group, said aromatic acyl group said heterocyclic acyl group, an aralkanoyl group or an aralkenoyl group); and U represents said group of formula >CH_2, then

(i) when R^1 represents a hydrogen atom or a C_1-C_4 alkyl group, R^4 represents a C_6-C_{10} alkyl group, and

(ii) when R^4 represents a hydrogen atom, a C_1-C_4 alkyl group or a C_1-C_4 alkoxy group, R^1 represents a C_6-C_{10} alkyl group or said C_7-C_{13} aralkyl group.

29. A process according to any one of Claims 24 to 27, in which:

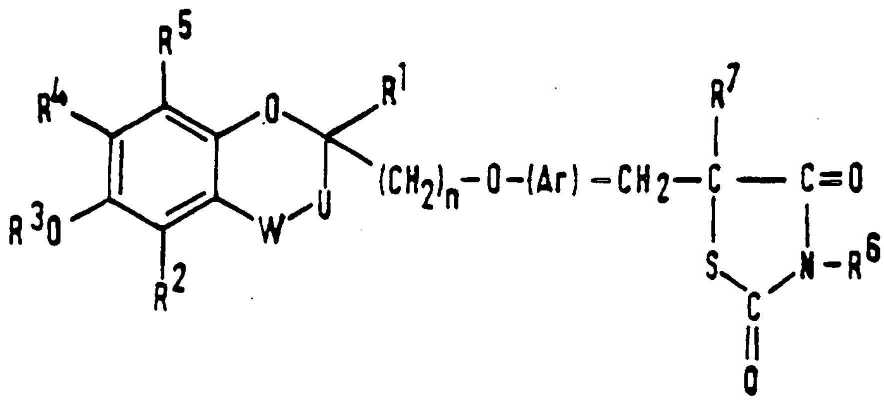
where: R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_4 alkyl group; and R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_4 alkyl group or a C_1-C_4 alkoxy group; and Ar represents a p-phenylene group; and W is a group of formula >CH_2, >C=O or >CH-OR^{11x}(where R^{11x} is as defined above): and U represents said group of formula >CH_2; and n is an integer from 1 to 3,

then

at least one of R^3, R^6 and R^7 represents said alkyl or substituted alkyl group.

Claims for contracting state : AT

1. A process for preparing compounds of formula (I):



(I)

[in which:

R^1 represents a hydrogen atom, a C_1-C_{10} alkyl group r a C_7-C_{13} aralkyl group;

R^2 represents a hydrogen atom or a C_1-C_6 alkyl group;

R^3 represents a hydrogen atom, a C_1-C_{22} alkanoyl group, a C_3-C_{22} alkenoyl group, a C_3-C_{22} alkynoyl group, a substituted C_1-C_{22} alkanoyl, C_3-C_{22} alkenoyl or C_3-C_{22} alkynoyl group having at least one of substituents (a), an aromatic acyl group, a heterocyclic acyl group, a group of formula $-SO_3R^8$ where

R^8 represents a hydrogen atom, an aralkyl group where the alkyl part is C_1-C_3 alkyl, a C_1-C_6 alkyl group or a C_1-C_6 alkyl group having at least one hydroxy or C_1-C_6 substituent,

a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one of substituents (b);

R^4 represents a hydrogen atom, a C_1-C_{10} alkyl group or a C_1-C_6 alkoxy group;

R^5 represents a hydrogen atom, a C_1-C_6 alkyl group or a C_1-C_6 alkoxy group;

R^6 and R^7 are the same or different and each represents a hydrogen atom, a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one of substituents (b);

Ar is a divalent carbocyclic aromatic group or a divalent heterocyclic aromatic groups;

W represents a $-CH_2$-group, a $>C=O$ group, a group of formula $>CH-OR^{11}$

wherein R^{11} represents a hydrogen atom, a C_1-C_{22} alkanoyl group, a C_3-C_{22} alkenoyl group, a C_3-C_{22} alkynoyl group, a substituted C_1-C_{22} alkanoyl, C_3-C_{22} alkenoyl or C_3-C_{22} alkynoyl group having at least one of substituents (a), an aromatic acyl group, a heterocyclic acyl group, a C_1-C_{10} alkyl group or a substituted C_1-C_{10} alkyl group having at least one of substituents (b).

or a group of formula $>C=N-O-R^{12}$

in which R^{12} represents a hydrogen atom, a C_1-C_{10} alkyl group, a C_1-C_{10} alkyl group having at least one of substituents (b), a C_1-C_{22} alkanoyl group, a C_3-C_{22} alkenoyl group, a C_3-C_{22} alkynoyl group, a substituted C_1-C_{22} alkanoyl, C_3-C_{22} alkenoyl or C_3-C_{22} alkynoyl group having at least one of substituents - (a), an aromatic acyl group, a heterocyclic acyl group or a group of formula $-CONR^9R^{10}$ where

R^9 and R^{10} are the sam or different and each r presents a hydrogen atom or a C_1-C_6 alkyl group or R^9 and R^{10}, together with the nitrogen atom to which they are attached, represent a heterocyclic group having from 5 to 7 ring atoms of which from 1 to 3 atoms, including said nitrogen atom, are nitrogen, oxygen or sulphur hetero-atoms, said heterocyclic group being unsubstituted, or, where said ring atoms include an additional nitrogen hetero-atom, said additional nitrogen atom being unsubstituted or having a single substituent selected from substituents (e);

U represents a $-CH_2$-group;

or

W and U together represent a group of formula $-CH=CH-$;

or

when W represents a carbonyl group or said group of formula $>C=N-OR^{12}$, U, R^1 and the carbon atom to which R^1 is attached together represent a group of formula $-CH=C<$;

n is an integer of from 1 to 3;

said aryl groups and the aryl parts of said aralkyl, aralkyloxycarbonyl, aromatic acyl, aromatic acyloxy and divalent aromatic groups being C_6-C_{10} carbocyclic aryl groups which are unsubstituted or have at least one of substituents (c);

said heterocyclic groups, heterocyclic parts of said heterocyclic acyl and acyloxy groups and said divalent heterocyclic aromatic groups have from 5 to 10 ring atoms, of which from 1 to 5 are nitrogen, oxygen or sulphur hetero-atoms, said heterocyclic groups being unsubstituted or having at least one of substituents (d);

said substituents (a) being aryl groups, carboxy groups, C_2-C_6 alkoxycarbonyl groups or aralkyloxycarbonyl groups;

said substituents (b) being hydroxy groups, C_1-C_6 alkoxy groups, aryl groups, C_1-C_{22} alkanoyloxy groups, C_3-C_{22} alkenoyloxy groups, C_3-C_{22} alkynoyloxy groups, substituted C_1-C_{22} alkanoyloxy, C_3-C_{22} alkenoyloxy or C_3-C_{22} alkynoyloxy groups having at least one of substituents (a), aromatic acyloxy groups, heterocyclic acyloxy groups, groups of formula $-COOR^8$ where R^8 is as defined

above and groups of formula $-CONR^9R^{10}$ where R^9 and R^{10} are as defined above;

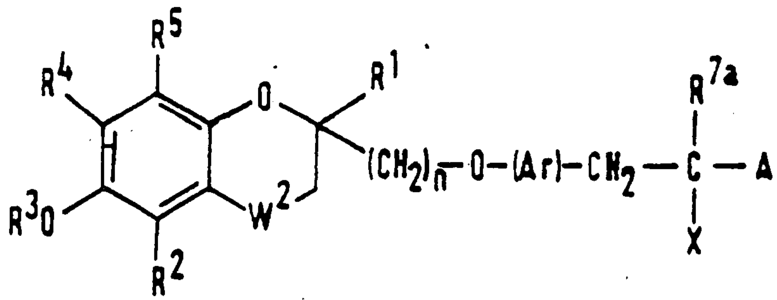
said substituents (c) being C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups, C_1-C_6 alkyl groups having at least one halogen substituent, halogen atoms, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups in which each alkyl part is C_1-C_6, nitro groups, cyano groups, groups of formula $-CONR_2$ - (where R represents a C_1-C_6 alkyl group or an aryl group) or hydroxy groups;

said substituents (d) being C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups or doubly bonded oxygen atoms; and

said substituents (e) being C_1-C_6 alkyl groups, C_1-C_6 alkanoyl groups, C_3-C_6 alkenoyl groups or C_3-C_6 alkynoyl groups;]

and pharmaceutically acceptable salts thereof, which comprises the steps:

(a) reacting a compound of formula (II):



(II)

(wherein:

R^1, R^2, R^3, R^4, R^5, n and Ar are as defined above;

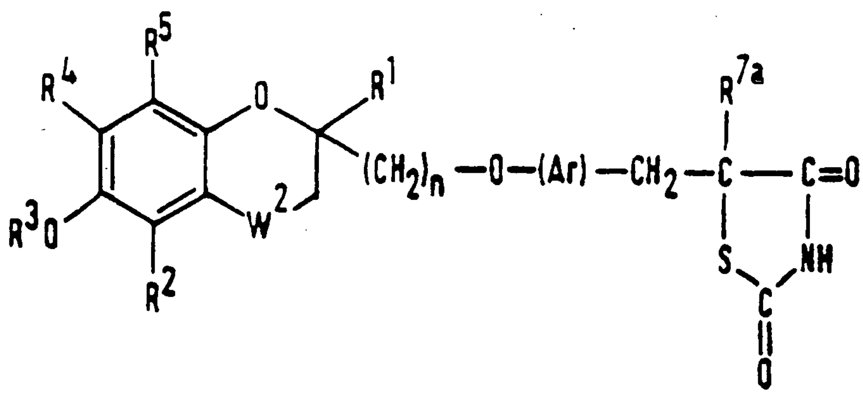
R^{7a} represents a hydrogen atom or an unsubstituted C_1-C_{10} alkyl group;

W^2 represents a methylene group or a carbonyl group;

A represents a cyano group, a carboxy group, a C_2-C_7 alkoxycarbonyl group, a carbamoyl group or a group of formula -COOM where M represents a cation; and

X represents a halogen atom)

with thiourea and hydrolysing the product to give a compound of formula (IV):



(IV)

(in which R^1, R^2, R^3, R^4, R^5, R^{7a}, n, Ar and W^2 are as defined above:

(b) if necessary, converting W^2 to another group represented by W or the methylene group at the 3-chroman position to another group represented by U;

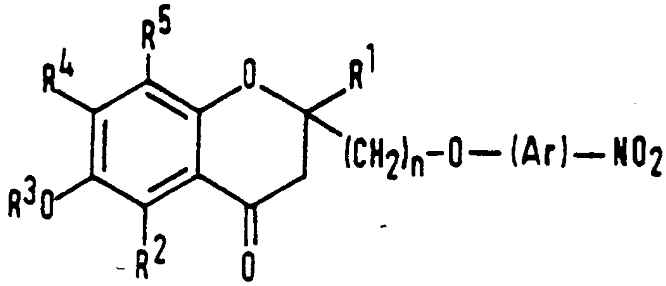
(c) if necessary, converting R^{7a} and/or the hydrogen atom at the 3-thiazolidine position to other groups represented by R^7 and R^6 respectively;

(d) if necessary, acylating and/or hydrolising the group $-OR^3$; and

( ) if necessary, salifying the product.

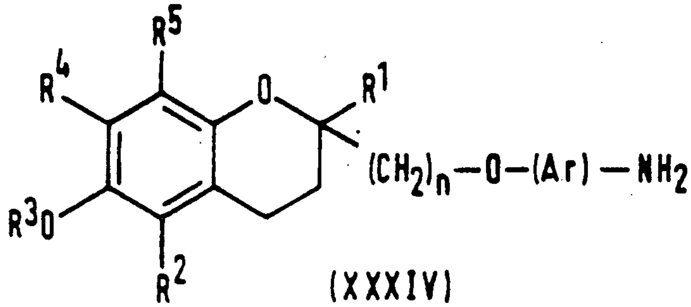
2. A process as claimed in Claim 1, wherein said compound of formula (II) is prepared by:

(i) in any order, subjecting of compound of formula (XLIX):



(XLIX)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 1) to the steps: reduction of the oxo group at the chroman-4 position to a hydroxy group, removing that hydroxy group and a 3-hydrogen atom to give a corresponding 2 H-chromene compound and hydrogenating the chromene double bond: and reducing the nitro group to an amino group, thereby giving a compound of formula (XXXIV):



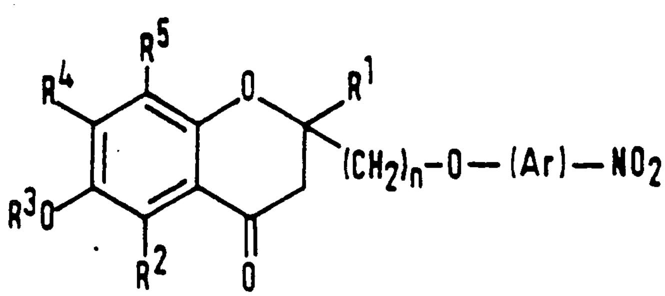
(XXXIV)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 1); and

(ii) diazotizing said compound of formula - (XXXIV) and subjecting the diazotized compound to a Meerwein arylation reaction with a compound of formula $CH_2=CR^{7a}A$ (where R^{7a} and A are as defined in Claim 1) to give said compound of formula (II)

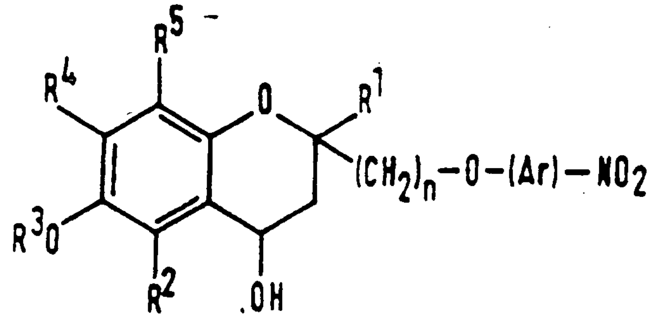
3. A process as claimed in Claim 1, which comprises the steps:

(i) reducing a compound of formula (XLIX):



(XLIX)

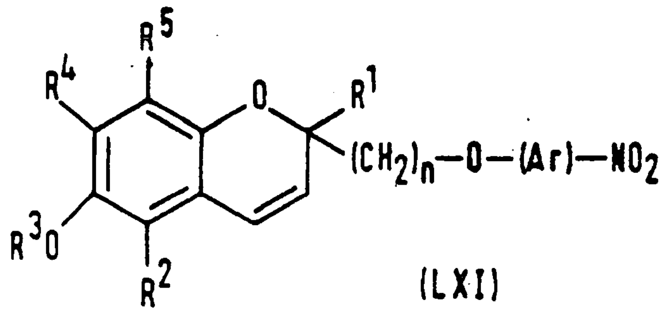
(in which R^1, R^2, R^3, R^4, R^5, n, and Ar are as defined in Claim 1) to give a compound of formula (LIX):



(LIX)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 1);

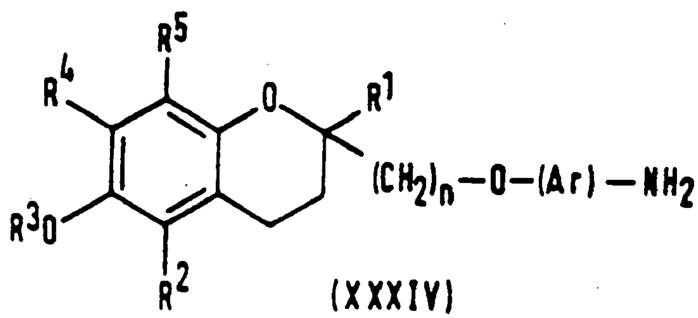
(ii)dehydrating said compound of formula (LIX), to give a compound of formula (LXI):



(LXI)

(in which R^1, R^2, R^3, R^4, R^5,n and Ar are as defined in Claim 1):

(iii) hydrogenating said compound of formula - (LXI), to give a compound of formula (XXXIV):



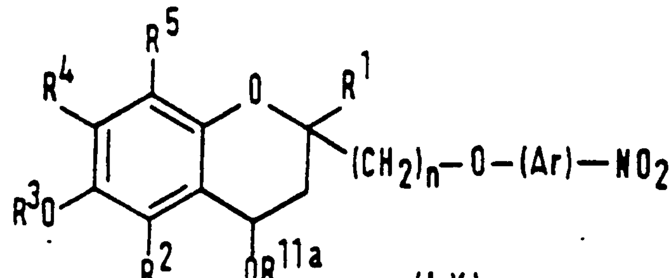
(XXXIV)

(in which R^1, R^2, R^3, R^4, R^5,n and Ar are as defined in Claim 1); and

(iv) subjecting said compound of formula - (XXXIV) to step (a) and, if necessary, steps (b) to - (e) as defined in Claim 1.

4. A process as claimed in Claim 3, wherein the dehydration of step (ii) is effected by

(ii-a) acylating said compound of formula (LIX), to give a compound of formula (LX):



(LX)

(in which R^1, R^2, R^3, R^4, R^5, n and Ar are as defined in Claim 3 and R^{11a} represents an acyl group); and

(ii-b) eliminating an acid of formula R^{11a}-OH from said compound of formula (LX), to give said compound of formula (LXI).

5. A process as claimed in Claim 1, in which:

R^1 represents a hydrogen atom or a C_1-C_{10} alkyl group;

R^2 represents a hydrogen atom or a C_1-C_3 alkyl group;

R^3 represents a hydrogen atom, a sulpho group, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one of substituents (g), a group of formula R^{13} -$(CH_2)_m$-CO-, where

R^{13} represents a phenyl group or a phenyl group having at least one of substituents (g), and m is an integer from 1 to 5.

a group of formula Het-CO-,where

Het represents a heterocyclic group having 5 or 6 ring atoms, of which 1 to 3 are nitrogen, oxygen or sulphur hetero-atoms, said heterocyclic group being unsubstituted or having at least one C_1-C_5 alkyl substituent,

a C_1-C_5 alkyl group, a C_1-C_5 alkyl group substituted by a group of formula -COOR^{8a}, where

R^{8a} represents a hydrogen atom, a C_1-C_5 alkyl group or an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_5,

a C_2-C_5 hydroxyalkyl group, an alkoxyalkyl group where both th alkoxy part and the alkyl part are C_1-C_5, a C_2-C_5 alkyl group substituted by a group of formula -O-CO-R^{83}, where

R^{83} represents a C_1-C_{10} alkyl group, a phenyl group, a phenyl group having at least one of substituents (g) or a heterocyclic group Het, as defined above.

or a C_1-C_3 alkyl group substituted by a single substituent selected from substituents (h);

said substituents (f) being phenyl groups, carboxy groups, C_2-C_6 alkoxycarbonyl groups or benzyloxycarbonyl groups;

said substituents (g) being C_1-C_5 alkyl groups, trifluoromethyl groups, C_1-C_5 alkoxy groups, halogen atoms, nitro groups, amino groups, hydroxy groups or dialkylamino groups where each alkyl part is C_1-C_5;

said substituents (h) being alkylcarbamoyl groups where the alkyl part is C_1-C_4, dialkylcarbamoyl groups where each alkyl part is C_1-C_4, 1-pyrrolidinylcarbonyl groups, piperidinocarbonyl groups or morpholinocarbonyl groups;

R^4 represents a C_1-C_{10} alkyl group or a methoxy group;

R^5 represents a hydrogen atom, a C_1-C_5 alkyl group or a methoxy group;

R^6 and R^7 the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group, a C_1-C_5 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined above, a C_2-C_5 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a group of formula -O-CO-R^{83} (where R^{83} is as defined above), or a C_1-C_3 alkyl group having a single substituent selected from substituents (h);

Ar represents a o-phenylene, m-phenylene or p-phenylene group or a pyridine-diyl group which is

attached to the part of said compound of formula -(I) of formula $-(CH_2)_n-O-$at its 2-position and is attached to the $-CH_2$-thiazolidine group at its 5-or 6-position, said phenylene and pyridine-diyl groups being unsubstituted or having a C_1-C_5 alkyl substituent;

W represents a group of formula $-CH_2-$, >C=O, >CH-OR''or >C=N-OR[12] where

R[11] represents a hydrogen atom, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one substituents (g), a group of formula $R^{13}-(CH_2)_m-CO-$ where R[13] and m are as defined above or a group of formula Het-CO-where Het is as defined above, and

R[12] represents a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_{10} alkyl group having at least one of substituents (j), a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f), an arylcarbonyl group wherein the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or has at least one of substituents -(g), or said group of formula $R^{13}-(CH_2)_m-CO-$or Het-CO-; and

said substituents (j) being hydroxy groups, C_1-C_5 alkoxy groups, phenyl groups, phenyl groups having at least one of substituents (g), C_2-C_{11} alkanoyloxy groups, C_2-C_{11} alkanoyloxy groups substituted by a group of formula $-COOR^{9a}$ where R^{9a} is as defined above, C_3-C_{11} alkenoyloxy groups substituted by a group of formula $-COOR^{9a}$ where R^{9a} is as defined above, phenylalkenoyloxy groups where the alkenyl part is C_3-C_{10} and the phenyl part is unsubstituted or has at least one of substituents (g) benzoyloxy groups, benzoyloxy groups having at least one of substituents (g), groups of formula -$COOR^{9a}$ where R^{9a} is as defined above, benzyloxycarbonyl groups and groups of formula $-COR^9R^{10}$ where R^9 and R^{10} are as defined above; U represents

(i) where W represents a group of formula -CH_2-, >C=O, >CH_2OR^{11} or >C=N-OR[12], a group of formula $-CH_2-$,

(ii) with W, a group of formula -CH=CH-, or

(iii) where W represents a group of formula >C=O or >C=N-OR[14], in which R[14] represents any one of the acyl groups defined for R[12], with R[1] and the carbon atom to which R[1] is attached, a group of formula -CH=C<.

6. A process as claimed in Claim 5, in which:

R[1], R[2], R[4], R[8], Ar, W and U are as defined in Claim 5;

R[6] and R[7] both represent hydrogen atoms;

R[3] and R[11] are the same or different and each represents a hydrogen atom, C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents -(f) as defined in Claim 5, an arylcarbonyl group as defined in Claim 5, or a group of formula R^{13} -$(CH_2)_m$-CO-or Het-CO-where R[13], m and Het are as defined in Claim 5; and

R[12] represents any one of the groups or atoms defined for R[3] and R[11] or a C_1-C_6 alkyl group or a C_1-C_3 alkyl group having at least one of substituents (f) as defined in Claim 5.

7. A process as claimed in Claim 5, in which:

R[1], R[2], R[4], R[8], Ar, W and U are as defined in Claim 5;

R[3], R[6], R[7] and R[12] are the same or different and each represents a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_5 alkyl group substituted by a group of formula $-COOR^{9a}$ where R^{9a} is as defined in Claim 5, a C_2-C_5 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a group of formula -O-CO-R^{83} where R^{83} is as defined in Claim 5 or a C_1-C_3 alkyl group substituted by a single substituent selected from substituents (h) as defined in Claim 5; and

R[11] represents a hydrogen atom, an acetyl group or a benzoyl group;

or

R[12] represents a hydrogen atom, a C^1-C^6 alkyl group, a C_1-C_{10} alkyl group having at least one of substituents (k), a C_2-C_6 alkanoyl group, a C_2-C_{10} alkanoyl group having at least one of substituents -(l), a C_3-C_6 alkenoyl group, a C_3-C_6 alkenoyl group having at least one of substituents (l), a benzoyl group, a benzoyl group having at least one of substituents (m), a pyridinecarbonyl group, a furoyl group, a thenoyl group or a pyridinecarbonyl, furoyl or thenoyl group having at least one C_1-C_5 alkyl substituent;

said substituents (k) being hydroxy groups, phenyl groups, phenyl groups having at least one of substituents (m), C_2-C_6 alkanoyloxy groups, C_2-C_{10} alkanoyloxy or C_3-C_{10} alkenoyloxy groups substituted

by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 5, C_2-C_{10} alkenoyloxy groups substituted by a ph nyl group where the phenyl group is unsubstituted or has at least on of substituents (m), benzoyloxy groups, benzoyloxy groups having at least one of substituents (m), groups of formula -COOR^{8a} where R^{8a} is as defined in Claim 5 or substituents (h) as defined in Claim 5;

said substituents (l) being phenyl groups, carboxy groups, alkoxycarbonyl groups where the alkoxy part is C_1-C_5 or benzylloxycarbonyl groups; and

said substituents (m) being C_1-C_5 alkyl groups, C_1-C_5 alkoxy groups, halogen atoms or trifluoromethyl groups

8. A process as claimed in Claim 1, in which:

R^1 represents a methyl, ethyl, isobutyl, pentyl, hexyl, 3,3-dimethylbutyl, heptyl, 4,4-dimethylpentyl, octyl, 5,5-dimethylhexyl, nonyl, or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a substituted C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f), a benzoyl group, a benzoyl group having at least one of substituents (n), an aralkanoyl group of formula R^{15}-(CH$_2$)$_m$-CO-

where R^{15} represents a phenyl group or a phenyl group having at least one of substituents (n), and m is an integer from 1 to 5,

a pyridinecarbonyl group, a furoyl group, a thenoyl group, a C_1-C_3 alkyl group, a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where

R^{8a} represents a hydrogen atom, a C_1-C_5 alkyl group or an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_5,

a C_2-C_3 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group or a methyl group having a single substituent selected from substituents (h);

said substituents (f) being phenyl groups, carboxy groups, C_2-C_6 alkoxycarbonyl groups or benzyloxycarbonyl groups;

said substituents (n) being C_1-C_5 alkyl groups, C_1-C_5 alk xy groups or halogen atoms;

R^4 represents a C_1-C_{10} alkyl group;

R^5 represents a hydrogen atom or a C_1-C_3 alkyl group;

R^6 and R^7 are the same or different and each represents a hydrogen atom, a C_1-C_3 alkyl group; a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined above, a C_2-C_3 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group, or a methyl group substituted by a single substituent selected from substituents (h);

said substituents (h) being alkylcarbamoyl groups where the alkyl part is C_1-C_4, dialkylcarbamoyl groups where each alkyl part is C_1-C_4, 1-pyrrolidinycarbonyl groups, piperidinocarbonyl groups or morpholinocarbonyl groups;

Ar represents a o-phenylene, m-phenylene or p-phenylene group or a pyridine-diyl group which is attached to the part of said compound of formula -(I) of formula -(CH$_2$)$_n$-O-at its 2-position and is attached to the -CH$_2$-thiazolidine group at its 5-or 6-position, said phenylene and pyridine-diyl groups being unsubstituted or having a methyl substituent;

W represents a group of formula -CH$_2$-, >C=O >CH-OR^{11} or >C=N-OR^{12}, where;

R^{11} represents a hydrogen atom or any one of the acyl groups defined above for R^3; and

R^{12} represents a benzyl group, any one of the groups or atoms defined above for R^3, a pyridinecarbonyl group or a pyridinecarbonyl group having at least one C_1-C_5 alkyl substituent; and U represents

(i) where W represents a group of formula -CH$_2$-, >C=O, >CH-OR^{11} or > C=N-OR^{12}, a group of formula -CH$_2$-,

(ii) with W, a group of formula -CH=CH-, or

(iii) where W represents a group of formula > C=O, with R^1 and the carbon atom to which R^1 is attached, a group of formula -CH=C<.

9. A process as claimed in Claim 8, in which:

R^1, R^2, R^4, R^5, Ar, W and U are as defined in Claim 8;

R^6 and R^7 are both hydrogen atoms;

R^3 and R^{11} are the same or different and each represents a hydrogen atom, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of substituents (f) as defined in Claim 8, a benzoyl group,

a benzoyl group having at least one of substituents (n) as defined in Claim 8, a group of formula R^{15}-$(CH_2)_m$-CO-(where R^{15} and m ar as defined in Claim 8), a pyridinecarbonyl group, a furoyl group or a thenoyl group; and

R^{12} represents a hydrogen atom, a methyl group, a benzyl group, a t-butoxycarbonylmethyl group or any one of the acyl groups defined above for R^3 and R^{11}.

10. A process as claimed in Claim 8, in which::

R^1, R^2, R^4, R^5, Ar, W and U are as defined in Claim 8;

R^3, R^6 and R^7 are the same or different and each represents a C_1-C_3 alkyl group, a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 8, a C_2-C_3 hydroxyalkyl group, a C_1-C_5 alkyl group substituted by a C_1-C_5 alkoxy group, a C_2-C_5 alkyl group substituted by a C_2-C_4 alkanoyloxy or a benzoyloxy group, or a methyl group having a single substituent selected from substituents (h) as defined in Claim 8;

R^{11} represents a hydrogen atom;

R^{12} represents a hydrogen atom, a C_1-C_3 alkyl group having at least one of substituents (o), a C_2-C_4 alkanoyl group, a C_2-C_4 alkanoyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 8, an acryloyl group, an acryloyl group having a β-substituent selected from substituents (f), a benzoyl group, a benzoyl group having at least one of substituents (q), a pyridinecarbonyl group, a pyridinecarbonyl group having at least one C_1-C_5 alkyl substituent or any one of the groups defined above for R^3, R^6 and R^7;

said substituents (f) being phenyl groups, carboxy groups, C_2-C_5 alkoxycarbonyl groups or benzyloxycarbonyl groups;

said substituents (o) being carboxy groups or alkoxycarbonyl groups where the alkoxy part is C_1-C_5;

and

said substituents (q) being methyl groups, ethyl groups, methoxy groups or ethoxy groups.

11. A process as claimed in Claim 1 in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_5 alkanoyl group, C_3-C_5 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-

where R^{16} represents a hydrogen atom or a C_1-C_5 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula $R^{17}OOC.CH=CH$-CO-

where R^{17} represents a hydrogen atom, a C_1-C_5 alkyl group or a benzyl group,

a 2-, 3-or 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where

R^{8a} represents a hydrogen atom, a C_1-C_5 alkyl group or an alkoxyalkyl group where both the alkoxy part and the alkyl part are C_1-C_5;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are the same or different and each represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined above;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$ -O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula -CH_2-, >C=O, >C=N-OH, > C=N-OCH_2COOH or >C=N-OCOR^{18}

where R^{18} represents a C_1-C_5 alkyl group; and

U represents a group of formula -CH_2-.

12. A process as claimed in Claim 11, in which:

R^1, R^2, R^4, R^5, Ar and U are as defined in Claim 11;

R^3 represents a hydrogen atom, a C_1-C_5 alkanoyl group, a C_3-C_5 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-where R^{16} and m are as defined in Claim 11, a cis or trans-group of formula $R^{17}OOC.CH=CH$-CO-where R^{17} is as defined in Claim 11, or a 2-. 3-or 4-pyridinecarbonyl group;

R^6 and R^7 are both hydrogen atoms;

W represents a group of formula >C = NOR^{12} where

R^{12} represents a hydrogen atom, a group of formula $-(CH_2)_3COOR^{8a}$, $-CH_2COOR^{8a}$, $-C(CH_3)_2COOR^{8a}$, $-COCH_2CH_2COOR^{8a}$ or -CO-CH = CH-COOR^{8a} where R^{8a} is as defined in Claim 11, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group or any one of the groups defined above for R^3, R^6 and R^7; and

n is 1 or 2.

13. A process as claimed in Claim 11, in which:

R^1, R^2, R^4, R^5, Ar and U are as defined in Claim 11;

R^3, R^6 and R^7 are the same or different and each represents a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 11;

W represents a group of formula >CH_2, >C = O or >C = NOR^{12};

R^{12} represents a hydrogen atom, a group of formula $-(CH_2)_3COOR^{8a}$, $-CH_2COOR^{8a}$, $-C(CH_3)_2COOR^{8a}$,-$COCH_2CH_2COOR^{8a}$ or -CO-CH = CH-COOR^{8a} where R^{8a} is as defined in Claim 11, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group or any one of the groups defined above for R^3, R^6 and R^7; and

n is 1 or 2.

14. A process as claimed in Claim 5, in which:

R_1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_{10} alkanoyl group, a C_3-C_{10} alkenoyl group, a C_1-C_{10} alkanoyl or C_3-C_{10} alkenoyl group having at least one of the substituents (f) as defined in Claim 5, an arylcarbonyl group as defined in Claim 5, a group of formula R^{13} -$(CH_2)_m$-CO-or Het-CO-where R^{13}, m and Het are as defined in Claim 5 or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 5;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 represents a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 5;

R^7 represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} wher R^{8a} is as defined in Claim 5;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula >CH_2, >C = O or >C = NOR^{12}, where

R^{12} represents a hydrogen atom, a group of formula $-(CH_2)_3COOR^{8a}$, $-CH_2COOR^{8a}$, $-C(CH_3)_2COOR^{8a}$, $-COCH_2CH_2COOR^{8a}$ or -CO-CH = CH-COOR^{8a} where R^{8a} is as defined in Claim 5, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 5;

U represents a group of formula -CH_2-; and

n is 1 or 2.

15. A process as claimed in Claim 5, in which:

R^1 represents a hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R_3 represents a hydrogen atom, a C_1-C_5 alkanoyl group, C_3-C_5 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-

where R^{16} represents a hydrogen atom or a C_1-C_4 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula R^{17}OOC.CH = CH-CO-

where R^{17} represents a hydrogen atom, C_1-C_4 alkyl group or a benzyl group,

a 2-, 3-pr 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula -COOR^{8a} where R^{8a} is as defined in Claim 5;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are the same or different and each represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 5;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula -CH_2-, >C=O or >C=N-OR^{12}, where

R^{12} represents a hydrogen atom, a group of formula -$(CH_2)_2COOR^{8a}$, -CH_2COOR^{8a}, -$C(CH_3)_2COOR^{8a}$, -$COCH_2CH_2COOR^{8a}$ or -CO-CH=CH-$COOR^{8a}$ where R^{8a} is as defined in Claim 5, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group, a C_1-C_4 alkyl group, a C_1-C_4 alkyl group substituted by a phenyl group where the phenyl group is unsubstituted or has at least one of substituents (n), or any one of the groups defined above for R^3, R^6 and R^7;

said substituents (n) being C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or halogen atoms; and

U represents a group of formula -CH_2-.

16. A process as claimed in Claim 5, in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl, or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_1-C_4 alkanoyl group, a C_3-C_4 alkenoyl group, a cinnamoyl group, a group of formula $R^{16}OOC(CH_2)_mCO$-

where R^{16} represents a hydrogen atom or a C_1-C_4 alkyl group and m is an integer from 1 to 5,

a cis-or trans-group of formula R^{17}OOC.CH=CH-CO-

where R^{17} represents a hydrogen atom, a C_1-C_4 alkyl group or a benzyl group,

a 2-, 3-or 4-pyridinecarbonyl group or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 5;

R^4 represents a hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are the same or different and each represents a hydrogen atom or a C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$ where R^{8a} is as defined in Claim 5;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$-O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula -CH_2-, >C=O or >C=N-OR^{12} where

R^{12} represents a hydrogen atom, a group of formula -$(CH_2)_2COOR^{8a}$, -CH_2COOR^{8a}, -$C(CH_3)_2COOR^{8a}$, -$CCH_2CH_2COOR^{8a}$ or -CO-CH=CH-$COOR^{8a}$ where R^{8a} is as defined in Claim 5, an acetyl group, a cinnamoyl group, a benzoyl group, a pyridinecarbonyl group, a C_1-C_4 alkyl group, a C_1-C_4 alkyl group substituted by a phenyl group where the phenyl group is unsubstituted or has at least one of substituents (n), or any one of the groups defined above for R^3, R^6 and R^7;

said substituents (n) being C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups or halogen atoms; and

U represents a group of formula -CH_2-.

17. A process as claimed in Claim 5, in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents C_1-C_3 alkyl group substituted by a group of formula -$COOR^{8a}$, where R^{8a} is as defined in Claim 5;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl, or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are both hydrogen atoms;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula -$(CH_2)_n$ -O-or a pyridine-diyl group attached to said group of formula -$(CH_2)_n$-O-at the 2-position and to the -CH_2-thiazolidine group at the 5-position;

W represents a group of formula $-CH_2-$, $>C=O$, $>C=N-OH$, or $>C=N-O-(C_1-C_3$ alkyl)$-COOR^{8a}$ where R^{8a} is as defined in Claim 5;

U represents a group of formula $-CH_2-$; and

n is 1 or 2.

18. A process as claimed in Claim 5, in which:

R^1 represents a methyl, isobutyl, hexyl, heptyl, octyl, nonyl or 3,7-dimethyloctyl group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a group of formula $-CH_2-COOR^{8a}$ where R^{8a} is as defined in Claim 5;

R^4 represents a methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, 1,1,3,3-tetramethylbutyl, 1,1-dimethylbutyl or 1,1-dimethylpropyl group;

R^5 represents a hydrogen atom or a methyl group;

R^6 and R^7 are both hydrogen atoms;

Ar represents a p-phenylene group, a m-phenylene group having a methyl group at the position ortho to the position of attachment to the group of formula $-(CH_2)_n-O-$ or a pyridine-diyl group attached to said group of formula $-(CH_2)_n-O-$ at the 2-position and to the $-CH_2-$thiazolidine group at the 5-position;

W represents a group of formula $-CH_2-$, $>C=O$, $>C=N-OH$, or $>C=N-O-(C_1-C_3$ alkyl)$-COOR^{8a}$ where R^{8a} is as defined in Claim 5;

U represents a group of formula $-CH_2-$; and

n is 1 or 2.

19. A process as claimed in Claim 1, wherein the starting materials are so selected as to prepare:

5-[4-(6-Hydroxy-5, 7, 8-trimethyl-2-octylchroman-2-ylmethoxy)benzyl]thiazolidine-2, 4-dione;

5-{4-[6-Hydroxy-4-(E)-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione;

5-{4-[6-Acetoxy-4-(E)-acetoxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy]-benzyl}thiazolidine-2,4-dione;

α-{5-[4-(6-Carboxymethoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid;

α-{5-[4-(6-Carboxymethoxy-4-hydroximino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidin-3-yl}acetic acid; or

α, α'-{5-[4-(6-Carboxymethoxy-4-hydroxyimino-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine-3,5-diyl}diacetic acid;

or a pharmaceutically acceptable salts thereof.

20. A process according to any of the preceding Claims, in which:

where: R^3 represents said hydrogen atom, an unsubstituted C_1-C_6 alkanoyl group, an unsubstituted C_3-C_6 alkenoyl group, an unsubstituted C_3-C_6 alkynoyl group, said aromatic acyl group, said heterocyclic acyl group, an aralkanoyl group or an aralkenoyl group; and R^6 and R^7 both represent hydrogen atoms; and Ar represents a p-phenylene group; and W represents a group of formula $>CH_2$, $>C=O$ or $>CH-OR^{11x}$ (wherein R^{11x} represents a hydrogen atom, an unsubstituted C_1-C_6 alkanoyl group, an unsubstituted C_3-C_6 alkenoyl group, an unsubstituted C_3-C_6 alkynoyl group, said aromatic acyl group, said heterocyclic acyl group, an aralkanoyl group or an aralkenoyl group); and U represents said group of formula $>CH_2$, then

(i) when R^1 represents a hydrogen atom or a C_1-C_5 alkyl group, R^4 represents a C_6-C_{10} alkyl group, and

(ii) when R^4 represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, R^1 represents a C_6-C_{10} alkyl group or said C_7-C_{13} aralkyl group.

21. A process according to any one of the preceding Claims, in which:

where: R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group; and R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group; and Ar represents a p-phenylene group; and W is a group of formula $>CH_2$, $>C=O$ or $>CH-OR^{11x}$ (where R^{11x} is as defined above); and U represents said group of formula $>CH_2$; and n is an integer from 1 to 3,

then

at least one of R^3, R^6 and R^7 represents said alkyl or substituted alkyl group.

22. The use for the manufacture of a medicament for the treatment of blood disorders of a compound of formula (I) or a salt thereof as defined in any one of Claims 1-21.